

IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE

MEDA PHARMACEUTICALS, INC.,
 and CIPLA LTD.,
 Plaintiffs,
 v.
 APOTEX INC. and APOTEX CORP.,
 Defendants.

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CIVIL ACTION
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NO. 14-1453-LPS

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Wilmington, Delaware
 Wednesday, December 14, 2016
Bench Trial - Volume B

- - -

BEFORE: HONORABLE **LEONARD A. STARK**, Chief Judge

APPEARANCES:

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23 P R O C E E D I N G S

24 (REPORTER'S NOTE: The following trial was held
25 in open court, beginning at 3:08 p.m.)

1 THE COURT: Good afternoon.

2 (The attorneys respond, "Good afternoon, Your
3 Honor.")

4 THE COURT: Do we have any issues we need to
5 discuss before we continue with the examination?

6 MR. LOMBARDI: We apparently have a technical
7 issue, Judge, that they were working on resolving before you
8 came down.

9 THE COURT: Where do we stand?

10 MR. ARANA: We're trying to get ahold of them
11 again.

12 MR. LOMBARDI: We need the courtroom people,
13 something happened to the screen.

14 THE COURT: Okay. Do you know if they have been
15 called or do you need us to call them?

16 MR. LOMBARDI: We need to recall them. They
17 were here but I think we do need to recall them.

18 THE COURT: We will do that.

19 MR. EVENS: Your Honor, if I could approach?

20 THE COURT: Wait one second.

21 MR. EVENS: Evens.

22 THE DEPUTY CLERK: He is on his way.

23 THE COURT: In the meantime, is there something
24 we should discuss while we're waiting for them to come back?

25 MR. EVENS: Your Honor, Mark Evens again.

1 THE COURT: Yes.

2 MR. EVENS: When we left yesterday, we had,
3 plaintiffs had moved to introduce the four exhibits that we
4 used to impeach Dr. Wedner. We're still trying to work out
5 an accommodation with Apotex. We should be able to reach
6 that certainly by the next break, we hope.

7 THE COURT: All right. Thank you for the update
8 on that.

9 MR. EVENS: Thank you.

10 THE COURT: Are there any issues from defendants
11 other than the technical issue?

12 MR. KLEIN: No issues, Your Honor.

13 THE COURT: All right.

14 MR. KLEIN: One logistical issue is yesterday we
15 promised to given up updated openings slides so we do have
16 those slides.

17 THE COURT: Oh, okay. Please pass those up.

18 MR. KLEIN: I don't know. How many do you need?

19 THE COURT: Two, please.

20 MR. KLEIN: Two?

21 THE COURT: Yes. And, Mr. Klein, it is your
22 witness I believe. I have your hard copy of the slides.
23 Would we be able to get started or would you prefer to wait?

24 MR. KLEIN: We can -- yes, we can do that.

25 THE COURT: All right. Why don't we do that.

1 And if we need to stop to let the technical people do their
2 thing, just let me know.

3 MR. KLEIN: I can also try to put it on the
4 Elmo, if that is easier.

5 THE COURT: The old fashioned way, if you like,
6 but you can pass up a hard copy.

7 MR. KLEIN: A hard copy should be ...

8 THE COURT: Our assistant is here.

9 MR. KLEIN: It might not be worth trying. In
10 the meantime ...

11 (Witness retakes the witness stand.)

12 THE COURT: You do not need to be sworn. You
13 are under oath.

14 And are there hard copies of your presentation
15 up there?

16 THE WITNESS: I will take a look. Yes.

17 THE COURT: Mr. Klein, do you think we can do
18 this with the witness and me having a hard copy?

19 MR. KLEIN: I do think so, Your Honor.

20 THE COURT: All right. I don't know if there is
21 something you all can be helped with in the background while
22 we're doing this, but if there is, I promise it won't
23 distract me.

24 MR. KLEIN: Okay.

25 THE COURT: All right. Why don't you go ahead

Schleimer - direct

1 then.

2 ... ROBERT P. SCHLEIMER, having been previously
3 sworn as a witness, was examined and testified as follows ...

4 DIRECT EXAMINATION (Continued)

5 BY MR. KLEIN:

6 Q. Welcome back, Dr. Schleimer.

7 A. Thank you.

8 Q. Now, yesterday I forgot to ask you something. Have
9 you done work for Apotex in the past?

10 A. I have.

11 Q. What type of work?

12 A. I met with a couple lawyers representing Apotex a
13 couple times in order to explore whether I would be an
14 expert witness for them.

15 Q. When was that?

16 A. In April of 2010.

17 Q. And was that in connection with the litigation?

18 A. Yes.

19 Q. And were you compensated for your time?

20 A. I was.

21 Q. About how much did you make during that period?

22 A. About \$7500.

23 Q. Did you end up serving as an expert witness?

24 A. I did not.

25 Q. Now, let's go back to DDX-4.20, which is where I

Schleimer - direct

1 believe we left off last night. Do you have that in front
2 of you?

3 A. I do.

4 Q. We were talking about intranasal antihistamines. How
5 many intranasal antihistamines were FDA approved in the 2002
6 time frame?

7 A. There were two, azelastine and Levocabastine.

8 Q. Can you compare those two products?

9 A. Well, there were only a couple of studies that
10 compared them, and the one that I have as an example on the
11 slide is by Falser from 2001, and they concluded that
12 Azelastine was statistically superior in efficacy as judged
13 by both physicians and patients themselves.

14 Q. And were you referring to Falser 2001, which is
15 PTX-266, as well as Küsters, which is DTX-85?

16 A. Yes.

17 Q. If we go to DDX-4.21, were steroids successfully
18 combined with antihistamines before 2002?

19 A. Yes. In fact, it was probably the most common
20 combination prescribed since antihistamines and intranasal
21 steroids were both exceedingly popular drugs. In this slide
22 I have excerpted a study by Drouin, et al, where they tested
23 the effects of the combination and found that it was -- that
24 it improved the treatment of patients with seasonal allergic
25 rhinitis compared to the monotherapies.

Schleimer - direct

1 Q. And what drugs were at issue in that study?

2 A. Loratadine and beclomethasone dipropionate.

3 Q. Are you referring to PTX-333?

4 A. Yes.

5 Q. If we go to the next slide, DDX-4.22. Were there
6 other studies before 2002 combining steroids with
7 antihistamines?

8 A. Yes. Many. And this is one example of them. This
9 is Brooks in 1996, and they confirmed the overall
10 effectiveness of the combination of a steroid and
11 antihistamine and they concluded that it will provide very
12 satisfy level of comfort for most seasonal allergic rhinitis
13 patients and would be preferred, and they also suggested
14 that there were additive suppression symptoms with a
15 combination.

16 Q. And are we referring to PTX-332?

17 A. Yes.

18 Q. If we go to the next slide, which is DDX-4.23, did
19 you also review a reference published by Berger in 1999?

20 A. Yes.

21 Q. And does Berger teach anything with regard to
22 Azelastine combination therapy?

23 A. Yes. And, in fact, Berger in this paper actually
24 comes out and proposes that Azelastine could be used in
25 combination with intranasal corticosteroids as his

Schleimer - direct

1 recommendation to physicians.

2 Q. That is DTX-26; right?

3 A. Yes.

4 Q. And there were other studies combining oral
5 antihistamines with intranasal steroids before 2002; is that
6 right?

7 A. There were, and I think we'll discuss them a little
8 later.

9 Q. Let's go to DDX-4.24. Was fluticasone ever
10 co-formulated with another drug before 2002?

11 A. Yes. And this slide I think is a very important one
12 because it covers the precedent that was already in the
13 literature, which was to take the steroid drug, which is the
14 superior drug, but acts slowly, and combine it with a
15 rapidly acting drug, because steroids in asthma were the
16 best drugs available, but the problem was patients got
17 impatient. They didn't feel the effect and they would
18 sometimes not use it.

19 So what Advair was is a combination of a rapidly
20 acting bronchodilator that would allow patients to have
21 improved breathing immediately, and it was combined with a
22 steroid, and over many days or weeks the steroid would
23 progressively improve the disease. And so this was due to
24 the same type of complementary mechanisms of action,
25 combining a drug that worked quickly and a drug that worked

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1 effectively, but with a delay.

2 And by putting it in a single product, they also
3 believed that it improved adherence, which is another way of
4 saying compliance. Ultimately, this drug Advair ended up
5 being the largest selling respiratory drug of all time, I
6 believe.

7 Q. And was the drug well-known as of June 2002 as well?

8 A. Yes. It was well on its way to being a very popular
9 drug.

10 Q. Okay. And for this slide, are you referring to
11 DTX-77 and DTX-68?

12 A. Yes.

13 Q. Okay. If we go to the next slide, this is 4.25.
14 Let's now turn to your next background topic, which is the
15 patents-in-suit; right?

16 A. Yes.

17 Q. And let's go to DDX-4.26. Have you reviewed the '620
18 and '428 patents-in-suit which are DTX-136 and DTX-253?

19 A. Yes.

20 Q. And do you understand that these patents are held by
21 Cipla?

22 A. Yes.

23 Q. Do all of the asserted '620 patent claims require a
24 pharmaceutical formulation comprising Azelastine and
25 fluticasone in a nasal spray?

Schleimer - direct

1 A. Yes.

2 Q. And do you understand that Apotex has a formulation
3 expert who will testify about the excipients required by
4 that patent?

5 A. Yes. Dr. Donovan.

6 Q. And do all the asserted '428 patent claims cover
7 methods of treating seasonal allergic rhinitis with
8 basically the '620 patent formulation?

9 A. Yes.

10 Q. And what's the difference between seasonal and
11 non-seasonal allergic rhinitis?

12 A. Well, as I believe Dr. Accetta testified, seasonal
13 allergic rhinitis occurs seasonally. For instance, if a
14 patient were only allergic to birch pollen, they would only
15 have symptoms when the birch trees are booming whereas
16 perennial allergic rhinitis is typically when the person is
17 allergic to an allergen that's always in their environment.
18 It could be a cat or mold or something like that. So they
19 always have symptoms.

20 But mechanistically, they both work the same way
21 and they respond similarly to drugs.

22 Q. What date do you use for determining prior art?

23 A. June 14th, 2002.

24 Q. And, by the way, are the patent specifications for
25 the two patents materially similar for purposes of this

Schleimer - direct

1 case?

2 A. Yes.

3 Q. Let's go to DDX-4.27. Now, do you recognize this
4 demonstrative to be a portion of the '428 patent
5 specification?

6 A. Yes.

7 Q. Did the listed inventors claim to have invented
8 fluticasone?

9 A. No.

10 Q. And did they claim to have invented a method of using
11 fluticasone to treat seasonal allergic rhinitis?

12 A. No.

13 Q. Did they claim to have invented Azelastine?

14 A. No.

15 Q. And did they claim to have invented a method using
16 Azelastine to treat seasonal allergic rhinitis?

17 A. No.

18 Q. And is this confirmed by the snapshot on DDX-4.27
19 from DTX-253?

20 A. Yes.

21 Q. Now, if we go to 4.28, what did the inventors say
22 about treatment with fluticasone combined with Azelastine?

23 A. Well, they said what I believe was already clear at
24 that time, which was that it would be highly desirable to
25 combine an antihistamine with a steroid.

Schleimer - direct

1 Q. In a pharmaceutically acceptable formulation?

2 A. Yes.

3 Q. And does the patent disclose any new clinical data to
4 support combining Azelastine with fluticasone?

5 A. No. There are no clinical data.

6 Q. Did the patent disclose testing as to whether these
7 drugs are compatible or incompatible with one another?

8 A. No.

9 Q. Do the patents disclose any recommended dosing
10 information for the combination?

11 A. No.

12 Q. If we go to the next slide, which is DDX-4.29.

13 How does the '428 patent describe the
14 therapeutic effect of combining the two drugs, Azelastine
15 and fluticasone?

16 A. Well, interestingly, it states that the two
17 therapeutic agents could be administered simultaneously
18 either in the same or different formulations and either
19 separately or sequentially. And in those cases, would
20 obtain a synergistic therapeutic effect.

21 Q. So according to the patent, do you need a
22 co-formulation of the two drugs to achieve what they called
23 a synergistic therapeutic effect?

24 A. No.

25 Q. And, by the way, does the patent provide any data

Schleimer - direct

1 that shows synergy when combining these two agents?

2 A. No.

3 Q. Could you go to the next slide, which is 4.30. Are
4 you generally familiar with the prosecution history?

5 A. Yes.

6 Q. And did the examiner initially find the
7 co-formulations claimed by the '620 patent to be obvious or
8 not obvious?

9 A. Obvious.

10 Q. And are you referring to DTX-137?

11 A. Yes.

12 Q. Now, if you go to slide 4.31, did Cipla respond to
13 that action by the PTO by submitting arguments and
14 declarations?

15 A. Yes. They submitted something called a Chopra
16 declaration, which argued that there was commercial
17 success and an unmet need and unexpected superiority of the
18 product.

19 Q. Okay. For the unexpected superiority, was that
20 declaration by Dr. Rajan and Maus?

21 A. Yes.

22 Q. All right. And, again, we're at DTX-137; is that
23 right?

24 A. Yes.

25 Q. Now, we were just talking about the prosecution

Schleimer - direct

1 history for the '620 patent. If we go to DDX-4.32, why did
2 the examiner allow the '428 patent?

3 A. The same reason.

4 Q. And is that DTX-307?

5 A. Yes.

6 Q. All right. Now, let's turn to your obviousness
7 opinions. And on DDX-4.33, we have your outline here.

8 Is the first several level of ordinary skill in
9 the art?

10 A. Yes.

11 Q. All right. Let's talk about that. It's on DDX-4.34.
12 What is the relevant art?

13 A. The relevant art is the study and the treatment of
14 allergic rhinitis.

15 Q. And were you asked to define a person of ordinary
16 skill in the art from a clinical perspective?

17 A. I was.

18 Q. And what is your definition?

19 A. My definition is that it would be a person with an
20 advanced degree, an M.D., a Ph.D. or a pharm D in that
21 field, the field of allergy immunology or pharmacology or an
22 equivalent field as well as three additional years in either
23 treatment or the research for treatments of allergic
24 rhinitis, preferably with experience with steroids and
25 antihistamines.

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1 Q. Do you understand that a person of ordinary skill in
2 the art for these patents could also be a formulator and
3 Apotex has another expert who will talk about that?

4 A. Yes.

5 Q. Now, were you a person of ordinary skill in the art
6 as of June 2002 under your definition?

7 A. Yes.

8 Q. Do you understand that Meda's experts have a
9 different definition?

10 A. Yes. They think that an M.D. is required for a
11 person of skill in the art.

12 Q. Okay. Do you agree?

13 A. No.

14 Q. Do you -- have you taught M.D.s how to treat allergic
15 rhinitis?

16 A. Yes. As I testified earlier, I regularly teach
17 clinical fellows learning to practice allergy about the
18 pathologic mechanisms and the treatments of allergic
19 diseases, including allergic rhinitis.

20 Q. And do you actually supervise individuals who satisfy
21 the definition of a person of ordinary skill in the art
22 under Meda's definition?

23 A. Yes. Our clinic, which is one of the largest
24 academic clinics in the country, is one that I'm ultimately
25 responsible for administratively.

Schleimer - direct

1 Q. And have you published about allergic rhinitis?

2 A. I have.

3 Q. Now, most scientists in pharmaceutical companies who
4 work on drug development for allergic rhinitis drugs, do
5 they have an M.D.?

6 A. Probably not. I can't tell you precisely, but in my
7 experience, some have an M.D., some who are in industry and
8 developing drugs. Most do not.

9 Q. All right. And did either of the listed inventors
10 have an M.D.?

11 A. No.

12 Q. So do you think a person of ordinary skill in the art
13 as of 2002 would need to have an M.D. in order to understand
14 the patents-in-suit and the issues in this case?

15 A. I do not.

16 Q. Would your opinions in this case change if a person
17 of ordinary skill in the art were defined to require an
18 M.D.?

19 A. No. I think as long as the M.D. was treating
20 patients with allergic disease and had experience in that,
21 it would be obvious to them that combining these two drugs
22 was desirable.

23 Q. Let's turn to the key prior art on which you relied.
24 The table of contents is DDX-4.35, but let's move to
25 DDX-4.36.

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1 Can you describe the prior art that you relied
2 on and is reflected in this slide?

3 A. Yes. One important piece of prior art is the
4 approval by the FDA of Flonase, which contains fluticasone
5 in 1994.

6 Q. And what was Flonase indicated for?

7 A. Flonase was approved for the management of nasal
8 symptoms of seasonal and perennial allergic and non-allergic
9 rights.

10 Q. You're referring to DTX-33?

11 A. Yes.

12 Q. So let's go to DDX-4.37. What's the next prior art
13 reference that you are relying on?

14 A. This is the approval in 1996 of Astelin, which
15 contains Azelastine. It was approved by the FDA for
16 intranasal administration for the treatment of the symptoms
17 of seasonal allergic rhinitis.

18 Q. And is that DTX-22?

19 A. Yes.

20 Q. Let's go to DDX-4.38. Were you here for Dr.
21 Accetta's testimony yesterday?

22 A. Yes.

23 Q. And were you here for Dr. Wedner's testimony?

24 A. Yes.

25 Q. Do you rely on their testimony to support your

Schleimer - direct

1 opinion?

2 A. I do.

3 Q. How so?

4 A. Well, both of them testified that shortly after
5 Astelin became available to practicing allergists, they used
6 it in combination with Flonase as an effective conjunctive
7 therapy.

8 Q. And here, are you citing DTX-1 through 10?

9 A. Yes, and there is an excerpt from one of his charts
10 which was shown yesterday.

11 Q. Let's move on to DDX-4.39.

12 What is the next key prior art reference?

13 A. I think this is a very important piece of information
14 in the case because this patent application by Cramer, et al
15 from the Proctor & Gamble company essentially describes the
16 invention in my opinion.

17 They wanted to combine a glucocorticoid or
18 steroid in an intranasal drug, and they listed about six
19 different possible steroids, with what they called a
20 leukotriene inhibiting antihistamine.

21 So at that time, already by '97, it was known,
22 what I said yesterday, which is that antihistamines, when
23 used topically or in the nose, can exert antiinflammatory
24 effects that are not found with oral versions in general.

25 So Cramer wanted to take an intranasal steroid

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1 and combine it with an intranasal antihistamine in order to
2 have a drug that with those complimentary actions, one that
3 worked quickly against the early phase and one that worked
4 well against the late phase.

5 And among the drugs, which there was a small
6 number, they specifically mentioned fluticasone and
7 azelastine.

8 Q. I don't think you mentioned the date. Was this 1997?

9 A. Yes. June 25th.

10 Q. And the applicant is Proctor and Gamble. What type
11 of company is that?

12 A. That is a pharmaceutical company.

13 Q. Now, in terms of -- how many steroids are listed
14 here?

15 A. I think it was six.

16 Q. And which were the most potent steroids in that list
17 as of June 2002?

18 A. As I testified yesterday, fluticasone, with
19 mometasone a little bit behind it.

20 Q. And in terms of the antihistamines, how many are
21 listed?

22 A. They list three, but only one of them was available
23 intranasally for topical administration, and that was
24 azelastine.

25 Q. So did Cramer identify a finite number of drugs for

Schleimer - direct

1 co-formulation in a pharmaceutical composition for nasal
2 administration?

3 A. Yes.

4 Q. In fact, what would have been the most obvious drug
5 combination or combinations to a person of ordinary skill in
6 the art reading Cramer in June of 2002?

7 A. Well, as discussed yesterday in the deposition of
8 Mr. Fuge, I agreed with what he said, which is that
9 fluticasone and azelastine would be the most obvious, not
10 the only but the most obvious combination because
11 fluticasone has the highest potency azelastine was the most
12 effective intranasal antihistamine.

13 Q. Is Cramer DTX-12?

14 A. Yes.

15 Q. Let's move on to DDX-4.40. What is the next prior
16 art reference?

17 A. This is another patent which had the same general
18 idea published for, submitted by Segal disclosing a
19 co-formulation of azelastine and fluticasone.

20 Q. I think you said it is a patent. Is it a patent
21 application?

22 A. It is an application, yes.

23 Q. Is it dated November 5th, 1998?

24 A. Yes.

25 Q. All right. If we go to the next demonstrative, which

Schleimer - direct

1 is DDX-4.41. Does this show portions of the Segal
2 reference?

3 A. Yeah. That is an excerpt of the application. So
4 Dr. Segal was at the Warner Lambert company, and they had
5 the same general idea, a little bit less specified.
6 Basically, they wanted to take an antiinflammatory steroid,
7 which as I explained, by far the most effective drugs for
8 the treatment of this disease. And they wanted to combine
9 it with a rapidly acting drug.

10 In this case, they included antihistamines, but
11 they included a few others as well. And they, like Cramer,
12 they specifically mentioned fluticasone and azelastine as
13 good candidate drugs for this combination.

14 Q. What kind of company is Warner Lambert?

15 A. Pharmaceutical company.

16 Q. Okay. To be clear, is Segal disclosing a
17 co-formulation of fluticasone and azelastine?

18 A. Yes.

19 Q. And is this DTX-21?

20 A. Yes.

21 Q. Let's go to the next reference on DDX-4.42.

22 Can you describe this reference, please?

23 A. Yes. So this is an excerpt from a paper by Charlie
24 Spector who is a leader in this field. And in my opinion,
25 he really laid it out. He said that the optimal treatment

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1 for patients with SAR, which is seasonal allergic rhinitis,
2 can only be achieved by managing both the early phase
3 response, the EPR, and the late phase response.

4 And he went on to say that the most
5 effective drugs for the early phase response were the H1
6 antihistamines and the most effective drugs for late phase
7 response were the corticosteroids.

8 So he concluded by saying the ideal
9 pharmacologic therapy would be a drug that contained both of
10 those drugs.

11 Q. I don't think you mentioned the date. Are we talking
12 March of 1999?

13 A. Yes.

14 Q. Is Spector DTX-50?

15 A. Yes.

16 Q. If we go to DDX-4.43. Is this another snapshot from
17 the Spector reference?

18 A. It is. And it's also relevant to the proceedings
19 today. You can see on the left the title of this editorial
20 is The Ideal Pharmacotherapy For Allergic Rhinitis. And
21 during this discussion, Dr. Spector points out that
22 decongestants, although they can have some beneficial
23 effects against congestion, have minimal effects against all
24 the other important symptoms of allergic rhinitis. So they
25 would not be a good complementary drug when combined with a

Schleimer - direct

1 steroid.

2 Chromium sodium and that family of drugs has to
3 be taken for weeks; and as Dr. Wedner testified, it has to
4 be taken four times a day. So it's not a practical
5 solution.

6 And the anticholinergic drugs such as
7 ipratropium, although they are good at drying runny nose,
8 they also doesn't address the other important symptoms of
9 allergic rhinitis, like sneezing, congestion, itchiness, et
10 cetera.

11 Q. So what does Dr. Spector suggests for managing both
12 the early and late phases of allergic rhinitis?

13 A. As I said in the previous slide, it was his opinion
14 that the ideal pharmacologic therapy would be a drug that
15 addresses the early and the late phase response, and that
16 would be an antihistamine and a steroid.

17 Q. Let's go to the next slide, which is DDX-4.44. What
18 is the next prior art reference you are relying on?

19 A. In 2001, the guidelines, called the ARIA guidelines,
20 that were discussed yesterday, which is a document of
21 about 180 pages that gives recommendations to practicing
22 physicians how to treat this disease, was released; and it
23 is specifically recommended the combination of steroid,
24 intranasal steroid and antihistamine cotherapy.

25 Q. And we'll take a closer look in a moment. But before

Schleimer - direct

1 we do so, how did allergy doctors and scientists view the
2 ARIA guidelines as of June 2002?

3 A. Well, as mentioned by Dr. Wedner, the ARIA guidelines
4 and the practice parameters are documents generated by
5 international leading experts, and they're found to be
6 generally very useful by practicing physicians.

7 Q. And we're referring to PTX-326; right?

8 A. Yes.

9 MR. KLEIN: Can we go to DDX-4.45.

10 BY MR. KLEIN:

11 Q. Can you explain what is on the screen?

12 THE COURT: And for the record, the screen is
13 now working happily.

14 THE WITNESS: Yes.

15 BY THE WITNESS:

16 A. This is a section of the treatment or management of
17 severe persistent disease.

18 Where it says in that first red box, a stepwise
19 approach is proposed. It is advised to use intranasal
20 glucocorticosteroids as a first line treatment. In other
21 words, a drug of first choice.

22 And if that doesn't manage the disease to add an
23 H1 antihistamine.

24 Q. And to be clear, is azelastine an H1 antihistamine?

25 A. Yes.

Schleimer - direct

1 Q. And because it is a long document, I'll identify the
2 page. It is PTX-326 at S251.

3 Okay. Let's turn to your obviousness analysis.

4 You offered an opinion on whether it was obvious
5 as of June 2002 to combine Flonase with Astelin to treat
6 allergic rhinitis.

7 A. I do. I think it was obvious and had been for
8 several years. Flonase was popular first-line therapy for
9 allergic rhinitis. It was already combined with
10 antihistamines routinely due to the complementary mechanisms
11 that I talked about.

12 Combining a fast acting drug and a slow acting
13 but more effective drug together.

14 The prior art encouraged the use of intranasal
15 antihistamines and the most effective one of the two
16 available were azelastine, and doctors such as Drs. Accetta
17 and Wedner and many others combined Flonase and Astelin in
18 their clinical practice with success.

19 Q. Did you also offer an opinion as to whether it was
20 obvious to a person of ordinary skill in the art as of June
21 2002 to co-formulate fluticasone and azelastine?

22 A. I do. I think co-formulation was logical, as was
23 discussed yesterday.

24 It is more convenient to use one bottle than two
25 bottles for patients with severe enough disease that they

Schleimer - direct

1 need both drugs.

2 And as I mentioned, with the experience with
3 Advair, convenient therapies improved patient compliance.

4 Two pharmaceutical companies had already
5 independently disclosed this specific co-formulation in
6 patent applications; that is Cramer and Segal.

7 And the successful co-formulation of fluticasone
8 with a rapid acting complementary drug in asthma was
9 extraordinarily successful by that time.

10 Q. So would a skilled artisan in 2002 have been
11 motivated to co-formulate fluticasone and azelastine in an
12 intranasal formulation?

13 A. Yes.

14 Q. And would a skilled artisan in 2002 have a reasonable
15 expectation that such a co-formulation would successfully
16 treat seasonal allergic rhinitis?

17 A. Yes.

18 Q. And you are citing DTX-21, 22, 33, 68 and 77; right?

19 A. Yes.

20 Q. Go to the next slide. We're on DDX-4.49 now. How
21 much fluticasone and azelastine would a skilled artisan use
22 in a co-formulated product?

23 A. Well, initial inclination would be just to use the
24 amounts per spray that were already available in the
25 approved products.

Schleimer - direct

1 Q. So what would that look like as a dosing regimen for
2 fluticasone?

3 A. Well, if you look on the left in green, fluticasone
4 was available at 50 micrograms per spray, and two regimens
5 that could be used are two sprays per nostril once a
6 day, or one spray per nostril twice a day, and either of
7 those regimens would produce 200 micrograms per day, daily
8 dose.

9 Q. Are these consistent with the FDA approved indication
10 for Flonase?

11 A. Yes.

12 Q. And what could the dosing for azelastine in a
13 co-formulated product look like?

14 A. Well, Astelin contains 137 micrograms per spray of
15 azelastine, and you could use the same two regimens, two
16 sprays per nostril once a day or one spray per nostril twice
17 a day, and that would yield 548 micrograms as the daily
18 dose.

19 Q. And is that an approved dosing regimen for
20 azelastine?

21 A. Yes. It's approved in the U.K. and other European
22 countries, but it's half of a dose that's approved in the
23 U.S.

24 Q. And so what would the co-formulated product look like
25 in terms of a regimen?

Schleimer - direct

1 A. Well, with these two regimens, I think a skilled
2 artisan would clearly prefer the one on the bottom right,
3 which is one spray per nostril twice a day for the reason
4 that azelastine only works for about a half a day.

5 Q. And are you referring to DTX-22 and 33 and PTX-326
6 for this slide?

7 A. Yes.

8 Q. Let's go to the next slide. Do you understand that
9 Meda is arguing that certain clinical testing in the prior
10 art teaches away or otherwise discourages co-formulating
11 fluticasone in azelastine?

12 A. Yes.

13 Q. And do you agree or disagree?

14 A. I disagree.

15 Q. And does this slide list some of the prior art
16 clinical studies that have been cited by the parties in this
17 case?

18 A. Yes.

19 Q. And have you specifically identified which of these
20 studies that Meda is relying on?

21 A. Yes. The ones that are shown with an asterisk.

22 Q. Okay. How many?

23 A. Four out of the seven.

24 Q. And did you list these clinical studies in
25 chronological order?

Schleimer - direct

1 A. Yes.

2 Q. So how many of the seven clinical studies on this
3 slide found at least some advantage to combining a steroid
4 with an antihistamine?

5 A. Five out of the seven.

6 Q. Now, let's take a look at the first two, Juniper 1989
7 and Benincasa 1994. Did those two studies find an advantage
8 in combining a steroid and an antihistamine?

9 A. No. However, in the Juniper study, they found a
10 strong trend for superiority in both eye symptoms and
11 sneezing that was not statistically significant.

12 In the Benincasa study, it was a large study,
13 but regrettably, it didn't have a placebo group or an
14 antihistamine alone group. And another issue with that
15 study is they only collected data after three weeks or
16 eight weeks of treatment. And as I've explained, the period
17 of time when you would expect to see the real advantage of
18 the combination is early on before the steroid is fully
19 effective when the antihistamine is making a big, a bigger
20 contribution proportionately.

21 Q. Now, the Juniper 1989 study used an oral
22 antihistamine called astemizole; is that right?

23 A. Yes.

24 Q. All right. Was that drug available on the market in
25 June of 2002?

Schleimer - direct

1 A. No. Astemizole was withdrawn from development.

2 Q. And do these two studies discourage others from
3 testing combinations of steroids and antihistamines?

4 A. No, not at all. As you can see, many studies
5 followed them.

6 Q. Okay. Let's go onto the Simpson 1994 study. Did
7 that find any advantage to combining a steroid with an
8 antihistamine?

9 A. It did. It found a statistically significant
10 improvement compared to both monotherapies for sneezing,
11 which is one of the hallmark symptoms of allergic rhinitis.

12 Q. And, by the way, I see the Simpson reference used
13 terfenadine as an oral antihistamine. Was that drug
14 available on the market in June of 2002?

15 A. No. That drug was withdrawn from the market due to
16 cardio vascular side effects.

17 Q. And the next two references, Drouin in 1995 and
18 Brooks in 1996. You touched on those earlier. Can you
19 just briefly summarize the conclusions from those two
20 studies?

21 A. Yes. Both of those studies showed a strong benefit
22 of the combination compared to the monotherapies, and I
23 think that the reason is that both of those studies looked
24 at the early time period after the initiation of treatment
25 from two days to four days, and, again, sneezing and itching

Schleimer - direct

1 in particular were symptoms that the combination was
2 superior in managing.

3 Q. The next study is Juniper 1997. Is that the same
4 Juniper from the Juniper 1989 reference?

5 A. Yes.

6 Q. Okay. And what are your comments with regard to the
7 Juniper 1997 reference?

8 A. Well, that's an interesting study because what they
9 did is, they gave the patients both drugs, instructed them
10 to take just one drug. Half of them took the antihistamine,
11 half the steroid. And they instructed them, if their
12 symptoms were not being adequately managed, to take the
13 other drug.

14 So the patients basically had the decision
15 whether to take the combination or not, and over two-thirds
16 of the patients in the study chose to combine both drugs to
17 adequately manage their symptoms.

18 Q. And --

19 A. So they concluded that at least 50 percent of
20 patients will need to take both types of medication in
21 combination to control symptoms adequately.

22 Q. Okay. And, finally, do you have comments with regard
23 to the Ratner 1998 reference on which Meda relies?

24 A. Yes. That there's a statement in the discussion that
25 says the combination was considered more effective according

Schleimer - direct

1 to some patient ratings.

2 Q. Now, did any of these clinical studies or the
3 references discussing the clinical studies tell skilled
4 artisans not to combine steroids with antihistamines?

5 A. No. There were no warnings in any of these studies.

6 Q. And did any of these references say that further
7 testing of steroids and antihistamines should not be
8 conducted?

9 A. No.

10 Q. And have you referred to DTX-40, DTX-248, PTX-41,
11 PTX-333, PTX-332, DTX-107 and PTX-330.

12 A. Yes.

13 Q. And do you have a slide summarizing how a skilled
14 artisan in 2002 would consider these clinical studies as a
15 whole?

16 A. Yes.

17 Q. All right, let's go to DDX-4.51. What are you
18 depicting on this slide?

19 A. Well, this shows the very same studies and the
20 timeline, but importantly, the one area of guidelines that
21 we've already discussed had the advantage of the information
22 in all of these studies prior to making their
23 recommendations, and they recommended the stepwise approach
24 that I discussed already, combining an intranasal steroid as
25 first line therapy with an antihistamine for control of

Schleimer - direct

1 patients with more severe disease.

2 Q. And to clarify, did any of these studies test an
3 intranasal steroid combined with an intranasal
4 antihistamine?

5 A. No.

6 Q. Were they all testing oral antihistamines?

7 A. Yes.

8 Q. And can clinical study results for steroid
9 antihistamine combination therapy vary depending on the
10 particular drugs that are being tested?

11 A. Yes.

12 Q. What about the patient population?

13 A. Yes.

14 Q. And can the results vary based on the timing of the
15 patient assessment?

16 A. Yes. As I discussed in this case particularly.

17 Q. Were there any clinical studies testing the
18 combination of fluticasone and azelastine in particular
19 before June 2002?

20 A. No. And in my view, that would have been the proper
21 study since that was the prior art as described by Drs.
22 Accetta and Wedner.

23 Q. And were there any prior art references that
24 discouraged doctors from using fluticasone with azelastine
25 to treat seasonal allergic rhinitis?

Schleimer - direct

1 A. No.

2 Q. And, in fact, as you testified, were doctors actually
3 combining Flonase and Astelin by June of 2002?

4 A. Yes.

5 Q. Now, Dr. Schleimer, were you here for the opening
6 statements?

7 A. I was.

8 Q. And did you see Meda's counsel put up a timeline that
9 had some additional clinical studies after June 2002?

10 A. Yes.

11 Q. Now, a skilled artisan in June 2002 wouldn't have
12 access to those studies; is that right?

13 A. No.

14 Q. But, nevertheless, have you reviewed them?

15 A. Yes, I have.

16 Q. And do any of those references change your opinions
17 in this case?

18 A. No. Two of them are reviews written by the same
19 group that was written by Nielsen, which is entered into
20 evidence, and expressed the same opinion that Nielsen did.
21 And two of them had actually original data, and in both of
22 them, the combination was found to be superior to the
23 individual monotherapies in some of the symptom routes.

24 Q. And have the ARIA guidelines since June 2002 ever
25 changed their recommendation as far as you have seen?

Schleimer - direct

1 A. As far as I know? Well, in 2010, the recommendation
2 is the same. The stepwise approach starting with intranasal
3 steroids and then adding on antihistamine.

4 Q. So viewing the prior art as a whole, does it teach
5 away or otherwise discourage skilled artisans from
6 co-formulating fluticasone with azelastine in a nasal
7 spray?

8 A. No, not at all. In fact, as I testified,
9 anti-inflammatory intranasal steroids and antihistamines are
10 still the -- among the most two popular classes of drugs
11 that are prescribed often together.

12 Q. Now, I just want to be clear. Are you saying that
13 all allergic rhinitis patients should be given both an
14 antihistamine and a steroid?

15 A. No. In fact, the ARIA guidelines as I mentioned, in
16 that section it's for patients with moderate to severe
17 disease that's not managed adequately just by the intranasal
18 steroid.

19 Q. So would that be the appropriate population for a
20 co-formulation of fluticasone and azelastine?

21 A. Yes. A group of patients with more disease.

22 Q. Now, let's wrap up. Can you summarize your
23 obviousness conclusions for the Court?

24 A. Yes. They're shown on this slide. Before 2002,
25 doctors combined Flonase with Astelin already, so the art

Schleimer - direct

1 was being practiced to treat allergic rhinitis due to
2 complementary mechanisms.

3 Two pharmaceutical companies had recognized
4 this and disclosed co-formulating fluticasone and azelastine
5 for nasal administration.

6 A pharmaceutical formulation comprising
7 fluticasone and azelastine in a nasal dosage form was
8 obvious in my view.

9 And it was also obvious to use this combination
10 to treat patients suffering from seasonal allergic rhinitis.

11 Q. Now, as you discussed in the beginning, if
12 appropriate, do you intend to come back during our rebuttal
13 case to address certain secondary consideration arguments
14 that may be presented?

15 A. Yes, I do.

16 MR. KLEIN: Okay. Your Honor, two things.
17 First, I understand that in DDX-4.25, I may notice half
18 listed all the exhibits, so I will read them again. DTX-40,
19 DTX-248, DTX-49, PTX-333, PTX-332, DTX-107 and DTX-140. And
20 I would move into evidence DTX-12, 21, 22, 26, 33, 34, 39,
21 40, 49, 50, 68, 72, 77, 85, 107, 136, 137, 140, 207, 248,
22 253, 258, 294, 306 -- I'm sorry, 307. PTX-66, PTX-325,
23 PTX-326, PTX-332, and PTX-333, and just for reference, I
24 used demonstrative exhibits DDX-4.00 through 4.52.

25 THE COURT: All right. Any objection to

Schleimer - cross

1 admission of the substantive exhibits?

2 MR. VARUGHESE: No objection, your Honor.

3 THE COURT: All right. Those are all admitted.

4 (The above-referenced exhibits were admitted
5 into evidence.)

6 MR. KLEIN: Thank you. No further questions at
7 this time.

8 THE COURT: All right. We'll have
9 cross-examination.

10 MR. VARUGHESE: May I approach?

11 THE COURT: You may approach, yes. Before you
12 do, Mr. Klein, do you have another set of your slide deck
13 that you just used with that witness? If you don't, if you
14 could get us one at a break, that would be helpful.

15 (Binders handed to the Court and to the
16 witness.)

17 MR. KLEIN: I will get you one.

18 THE COURT: I did have it, but I would like to
19 have another. You may proceed.

20 CROSS-EXAMINATION

21 BY MR. VARUGHESE:

22 Q. Good afternoon, Dr. Schleimer.

23 A. Good afternoon.

24 Q. Can we go to DDX-4.51, please.

25 Dr. Schleimer, you just testified regarding this

1 demonstrative slide; is that correct?

2 A. Yes.

3 Q. And you've outlined a number of studies there, and
4 it's true. And you say here that all of these studies
5 involved oral antihistamines; is that correct?

6 A. Yes.

7 Q. None of them involved a nasal antihistamine?

8 A. Correct.

9 Q. None of them involved azelastine in particular?

10 A. Yes.

11 Q. And that's because during this time period,
12 clinicians were overwhelmingly prescribing oral
13 antihistamines and not azelastine; isn't that correct?

14 A. Well, azelastine had just come onto the market in '97
15 and its market was growing, but it was still relatively
16 small compared to the other ones.

17 Q. Thank you. And it wasn't until 2008 -- I'm sorry. I
18 should ask you: Are you familiar with the Ratner 2008
19 study, Paul Ratner?

20 A. Yes.

21 Q. And it wasn't until that study nearly a decade after
22 this time period that azelastine and fluticasone tested
23 together were first public; is that right?

24 A. That's right. Even though doctors were practicing
25 the art of combining the art them, there was never a formal

1 study until that date.

2 Q. Indeed, if it was obvious to combine the two, it
3 stands to reason that it would have been tested in this time
4 period; isn't that correct?

5 A. There are a variety of reasons, many apparently
6 having to do with legal issues that influence that.

7 Q. Dr. Schleimer, you also mentioned a Fuge deposition;
8 is that right?

9 A. Yes.

10 Q. You were talking about Dennis Fuge?

11 A. Yes.

12 Q. You understand that he's an employee of Meda?

13 A. Yes.

14 Q. And you said he agreed with some statements that he
15 made?

16 A. I agreed when he said it was obvious to combine these
17 two drugs.

18 Q. Do you understand he made those statements in 2006?

19 A. That was the time of that deposition, yes.

20 Q. And I'm sorry. I just want to clarify. The
21 deposition was recent. He made those statements in 2006.

22 A. Correct. That was the time of interest in his recent
23 deposition.

24 Q. Sure. Just so we're on the same page.

25 And you understand he made those statements

Schleimer - cross

1 after visiting a company called Cipla in 2006?

2 A. Eventually he said, yes, that that was the case.

3 Q. And Cipla is a plaintiff in this case. You
4 understand that?

5 A. Yes.

6 Q. And Cipla is actually the patent owner in this case?

7 A. Yes.

8 Q. And Meda and Cipla are different companies.

9 Do you understand that?

10 A. I do.

11 Q. Okay. And do you understand that Mr. Fuge's company,
12 Meda, years prior to that, tried to make a combination
13 product but failed?

14 A. Yes.

15 MR. KLEIN: Objection.

16 THE COURT: I'm sorry?

17 MR. KLEIN: Beyond the scope of the direct.

18 MR. VARUGHESE: Your Honor, Dr. Schleimer
19 brought up that he agreed with that statement. I think it's
20 only fair that we have proper context around his knowledge
21 in such agreement.

22 THE COURT: Anything else?

23 MR. KLEIN: I think he said an issue of
24 formulation that would be addressed by other experts.

25 THE COURT: All right. I'm going to overrule

Schleimer - cross

1 the objection. It's fairly within the scope. You can
2 answer or ask another question.

3 BY MR. VARUGHESE:

4 Q. I believe you answered yes to my last question before
5 the objection.

6 A. Sorry. What was the question again?

7 Q. Did you understand that he made that -- he worked for
8 a company called Meda where several years before he made
9 that statement, they tried to make an azelastine fluticasone
10 combination product, but failed.

11 Do you understand that?

12 A. I have not been asked to judge all the formulation
13 efforts.

14 Q. Do you understand that his company tried to create a
15 combination --

16 A. I understand there are some claims that they did,
17 yes.

18 Q. And to be clear, sir, I'm not asking you about
19 formulation details. I understand you're not a formulation
20 expert. My question is: Do you understand that Dennis
21 Fuge's company tried to make a combination product several
22 years before that --

23 A. Yes. As Mr. Lombardi mentioned, they spent "two or
24 three days trying," with quotes.

25 Q. And if it was so obvious to Mr. Fuge, don't you

Schleimer - cross

1 think that he would have been able to come up with a
2 formulation?

3 A. That's not an issue that I've been asked to provide
4 testimony about.

5 Q. Okay. So switching gears a little bit, Dr.
6 Schleimer, before Cipla invented Duonase, there was never a
7 fixed dose mix of azelastine and fluticasone in one product;
8 is that correct?

9 A. To the to my knowledge.

10 Q. Anywhere in the world?

11 A. Correct.

12 Q. And before Cipla invented Duonase, there was actually
13 no fixed dose combination product comprising an
14 antihistamine and a steroid; is that correct?

15 A. Not to my knowledge.

16 Q. And, in fact, before Cipla invented Duonase, there
17 was no combination, two ingredient, active ingredient
18 combination product for the treatment of allergic rhinitis;
19 isn't that right?

20 A. Not to my knowledge. That doesn't mean there weren't
21 others, but I'm not aware.

22 Q. Okay. But you are not aware of that?

23 A. That's right.

24 Q. So in that regard, Duonase, when it was launched, was
25 a one of a kind product for the treatment of allergic

1 rhinitis; is that right?

2 A. Yes.

3 Q. Yet your testimony today is that it would have been
4 obvious for someone to make this invention before Cipla had?

5 A. Yes.

6 Q. You testified yesterday I believe that you are not a
7 physician; correct?

8 A. Correct.

9 Q. You don't prescribe medications?

10 A. I do not.

11 Q. And you don't treat patients in an office?

12 A. I do not.

13 Q. So you don't make decisions on how to adjust a dose,
14 titrate medications, things like that?

15 A. Not for prescription to individual patients, but I
16 talk about dosing all the time. I'm a pharmacologist and
17 that is an important issue in the use of drugs for treatment
18 of any disease and in particular rhinitis and asthma disease
19 that I'm interested in.

20 Q. Sure. What I mean is, in a clinical setting, you
21 don't assess a patient, review their chart, medication
22 history, and adjust dosages or drugs based on assessing
23 them; correct?

24 A. Correct.

25 Q. Yet your opinion, though, is that physicians and

Schleimer - cross

1 clinicians who do do that would find it obvious to combine a
2 fixed dose combination, azelastine and fluticasone?

3 A. Yes.

4 Q. Before this, litigation though, you have never
5 suggested to a physician that they should combine azelastine
6 and fluticasone; correct?

7 A. Not to my recollection.

8 Q. And no physician before this litigation has told you
9 that they were combining azelastine and fluticasone; is that
10 correct?

11 A. You know, in the late 90s, I was at Johns Hopkins and
12 my colleagues were using these classes of drugs and
13 discussing them on a regular basis. I was very aware of the
14 antiinflammatory effects of antihistamines because the group
15 that I was in had done considerable studies on these.

16 It was found that antihistamines could inhibit
17 mass cell responsive degranulation, release of leukotrienes.
18 There was a lot of interest in what are called off target
19 effects of antihistamines. The usual effects are blocking
20 the H1 histamine receptors. These drugs were able to
21 observe other antiinflammatory effects. So I don't remember
22 a specific conversation about combining these two specific
23 drugs, but we had great interest in the antiinflammatory
24 effects of antihistamines.

25 Q. Thank you.

Schleimer - cross

1 A. In fact, I have a patent that describes use of an
2 antihistamine for antiinflammatory effects.

3 Q. So, Dr. Schleimer, I saw your qualifications. You're
4 a highly respected individual in this field; and with due
5 respect, I'm going to try to ask you simple questions, and I
6 need simple answers unless I ask you more complex question.

7 So my question is simply no physician before
8 this litigation told you they were combining azelastine with
9 fluticasone; correct?

10 A. And my answer was I don't recall if they did in the
11 late 90s, but it wouldn't surprise me at all.

12 Q. That's fine. If you don't recall, that is a fine
13 answer.

14 A. So the answer is I don't know.

15 Q. And in this litigation, you are relying on Dr.
16 Accetta and his records to understand that a physician might
17 have been prescribing azelastine and fluticasone together;
18 correct?

19 A. That is one of the pieces of information, yes.

20 Q. There is no other physician records in this
21 litigation that you are relying on?

22 A. Well, there is the testimony of Dr. Wedner who was
23 doing the same thing.

24 Q. Sure, I understand that Dr. Wedner gave some
25 testimony in that regard. But you haven't reviewed any

Schleimer - cross

1 of his patient records; right?

2 A. No, but I believe of what he said.

3 Q. None of his patient records were in any of his
4 demonstratives?

5 A. Correct.

6 Q. And do you know whether he had prescribed those drugs
7 in a particular time scale for a administration?

8 A. He said he did.

9 Q. But you haven't seen any records?

10 A. We have established that, yes.

11 Q. And in formulating your expert report, you also
12 didn't review any of Dr. Accetta's prescription records; is
13 that correct?

14 A. I read his full deposition in which he discussed
15 those data.

16 Q. Now, you heard Dr. Accetta's testimony yesterday.
17 Were you in the courtroom?

18 A. I was.

19 Q. And he testified yesterday that based on his record,
20 I'm focusing on the records that are in evidence, there is
21 nothing to indicate a particular dosing sequence of the two
22 agents or particular time interval of the two agents. Isn't
23 that right?

24 A. Well, I heard it a little differently.

25 Q. Dr. Accetta admitted that or it was on the records

Schleimer - cross

1 themselves on several occasions that he prescribed these
2 agents on an as needed basis, the azelastine?

3 A. Well, he said that he prescribed them daily or as
4 needed. And my take from his testimony was that if your
5 symptoms get worse, start using it daily again. If they
6 resolve, stop using it. That is different from using it
7 willy-nilly. But that was my interpretation of what he
8 said.

9 Q. That is very helpful, Doctor. So that is right,
10 that is my interpretation, too. If a patient deemed it
11 necessary, he or she would add the azelastine, and if he or
12 she deemed it not necessary, they dropped the azelastine for
13 the time being; correct? And such an as needed dose -- and
14 I'm not suggesting it is willy-nilly, but such an as needed
15 dose or PRN dose is not a fixed dose regimen; correct?

16 A. Well, it's a fixed dose regimen for the duration of
17 the time that the patient is using both drugs daily which
18 could be weeks or even months.

19 Q. Or a day?

20 A. That would be unlikely, but or a day.

21 Q. Why would that be unlikely?

22 A. Well, it would be unlikely to resolve the symptoms so
23 quickly.

24 Q. And that kind of titration, that's the practice of
25 medicine, isn't it?

Schleimer - cross

1 A. I'm not sure what you are getting at.

2 Q. Are you familiar with the concept of dose titration?

3 A. Sure, I'm a pharmacologist.

4 Q. Isn't that dose titration? Instructing a patient to
5 raise or lower a dose of a drug or add or remove a drug from
6 a course of treatment, isn't that dose titration?

7 A. That can occur, yes.

8 Q. Sitting here today, you don't have any evidence to
9 present that shows that Dr. Accetta had any of his patients
10 on a fixed dose regimen of azelastine and fluticasone where
11 one drug was consistently taken before another and one drug
12 was taken consistently at the same time interval as the
13 other; is that correct?

14 A. My reading of his charts was that he was prescribing
15 both daily fluticasone and daily azelastine.

16 Q. In re-reviewing his charts, did you see any
17 instruction where he told the patient to take azelastine
18 before fluticasone or vice-versa?

19 A. No.

20 Q. Okay. In reading his charts, did you see any
21 indication -- strike that. Did you see any instruction
22 where he told a patient to take fluticasone within a certain
23 time period after taking azelastine or vice-versa?

24 A. No.

25 Q. Dr. Schleimer, what in your view is the closest prior

1 art to the patent in suit?

2 A. It is the conjunctive use of both intranasal
3 fluticasone and intranasal azelastine.

4 Q. And the only evidence of that use is Dr. Accetta's
5 record in this litigation?

6 A. As I said, Dr. Wedner also testified that he used
7 that same combination.

8 Q. Okay. Other than Dr. Wedner's oral testimony, you
9 don't have any records confirming that from Dr. Wedner;
10 correct?

11 A. Correct.

12 Q. And other than Dr. Wedner and Dr. Accetta's records,
13 you provided no other evidence of that prior use; right?

14 A. That's correct.

15 Q. So, Dr. Schleimer, you are familiar with the ARIA
16 guidelines; correct?

17 A. I have a working familiarity with it.

18 Q. In fact, you cited them in your demonstratives that
19 we just saw and you also cited them in your expert reports;
20 right?

21 A. Yes.

22 Q. Okay. And we'll get to it, but you highlighted a
23 phrase from those guidelines called stepwise therapy.

24 A. Yes.

25 Q. What Dr. Accetta was doing was stepwise therapy with

1 azelastine; correct?

2 A. It appears so, yes.

3 Q. I'm going to put the ARIA guidelines up so we can
4 take a look, but for your convenience, it is Tab 2 in the
5 book we provided you.

6 Can we go to page 120, please?

7 A. Did you say 120?

8 Q. 120, yes. So that would be the bottom right.

9 I'm sorry, Dr. Schleimer. Why don't you go to
10 S251. This was for our technical person.

11 A. (Witness complies.)

12 Q. Thank you. I want to direct your attention to the
13 left column, the lower part.

14 And if we can have that blown up?

15 This is a stepwise approach that we were
16 referring to; is that correct?

17 A. It is part of it.

18 Q. Now, you have opined in this case that the ARIA
19 guidelines would provide a motivation to a POSA -- I'm
20 sorry. Do you understand when I say a POSA that I am
21 referring to a person of ordinary skill in the art?

22 A. Yes.

23 Q. So the ARIA guidelines would motivate a POSA to
24 combine azelastine and fluticasone in a single formulation;
25 is that correct?

1 A. I'm opining that the ARIA guidelines made it clear
2 that the intranasal steroids were combined with
3 antihistamines as the primary recommendation of the ARIA
4 guidelines. Antihistamines in general.

5 Q. Is there anything in the ARIA guidelines that you
6 think would have suggested to a POSA to put azelastine and
7 fluticasone into a single formulation?

8 A. I did not see that specific recommendation.

9 Q. So staying right here. Number 2. It is advised to
10 use intranasal glucocorticosteroids as a first line
11 treatment. Correct?

12 A. Yes.

13 Q. First line treatment isn't for the
14 glucocorticosteroid to be combined with azelastine or any
15 other intranasal antihistamine?

16 A. That is correct.

17 Q. That is correct.

18 A. That's the drug of first choice.

19 Q. Sure. And later on, under 3, it says if the nose is
20 very blocked: Alternatively, intranasal decongestants for
21 less than 10 days.

22 A. Yeah, that is in the specific case where nasal
23 blockage is the major problem. As I mentioned,
24 decongestants are good in treating blockage but they don't
25 address the other symptoms such as sneezing, itching,

1 rhinorrhea.

2 Q. Sure. But given that the ARIA guidelines seem to
3 suggest that glucocorticosteroids can be added to intranasal
4 decongestants, would it also be your opinion that a single
5 formulation of those two agents would also have been obvious
6 at this time?

7 A. No, I don't think it would be obvious at all. In
8 fact, it wouldn't be appealing since you wouldn't be
9 complementing the steroids. As I mentioned, the steroids
10 work very slowly and the decongestant would only prevent
11 congestion early on. But if the patient had the other
12 symptoms such as sneezing and runny nose, combining them
13 would give you no extra advantage because those would not be
14 affected by the decongestant.

15 Q. So you just provided for me some other considerations
16 that weigh against combining these two agents; correct?

17 A. Yes. I don't think combining a decongestant with an
18 intranasal steroid would be particularly obvious.

19 Q. Now, in forming your opinions that combining
20 azelastine and fluticasone would be obvious, did you
21 consider any other factors that would weigh against such a
22 combination, just like you did here?

23 A. I couldn't think of any. I mean they're very
24 complementary drugs. You have the antihistamine with the
25 immediate effects against the early phase and you have the

1 steroid with the profound effects against the late phase.

2 So they seem perfectly complementary.

3 Q. So you didn't drawn any drawbacks?

4 A. I'll leave that to you to tell me what you think are
5 the drawbacks.

6 Q. I am just a lay lawyer. I'm asking you the question.
7 You formed an opinion.

8 A. Yes.

9 Q. You obviously are qualified as a pharmacologist. And
10 I'm asking you, when you concluded that it would have been
11 obvious to combine azelastine and fluticasone, did you also
12 consider potential drawbacks?

13 A. Well, they're both very safe drugs, and I, I think it
14 would be clearly worth the effort to try it.

15 Q. So switching gears. You identified some benefits of
16 combining azelastine with fluticasone; isn't that correct?

17 A. Yes.

18 Q. One benefit was that it would reduce the volume?

19 A. Are you talking about my declaration?

20 Q. Well, just your opinions in this case. Yes, your
21 expert report, your deposition.

22 A. I haven't testified at all about the volume.

23 Q. But you expressed that opinion in this case, right?

24 A. I believe it was mentioned in one of my declarations,
25 but --

Schleimer - cross

1 THE COURT: Hold on, Doctor.

2 Is there an objection?

3 MR. KLEIN: It's going beyond the scope of the
4 direct. He can answer this question but the questions along
5 the lines of the amount of liquid, I didn't get into that at
6 all.

7 THE COURT: Yes. What is the relevance?

8 MR. VARUGHESE: So, Your Honor, Dr. Schleimer
9 testified there were all these benefits to combining these
10 two. He testified he hasn't thought of any drawbacks. I'm
11 trying to get him to weigh both factors.

12 THE COURT: So you have some drawbacks to
13 suggest to him that you want to know if he considered?

14 MR. VARUGHESE: I'd like to with the drawbacks
15 and also whether or not the gains that he suggested was
16 modest, but I'm happy to move on with this line of
17 questioning if it pleases the Court.

18 THE COURT: Okay. It's up to you, but that's
19 fine. I haven't made a ruling.

20 MR. VARUGHESE: I understand.

21 BY MR. VARUGHESE:

22 Q. Dr. Schleimer, you said compliance would be a
23 benefit; right?

24 A. Yes.

25 Q. Okay. In your view, is that a significant benefit?

Schleimer - cross

1 A. One wouldn't know until they test it, but I believe
2 it would be a significant benefit as was the case with
3 Advair where compliance was clearly better.

4 Q. Would it be a significant benefit in this context,
5 allergic rhinitis and combining two nasal sprays?

6 A. I would have expected it before the priority date,
7 yes.

8 Q. So do you recall, in your deposition, when asked
9 about the benefits of combining this, you said they were all
10 modest?

11 A. Well, we're talking about therapeutic benefits.
12 Compliance is a benefit, functional benefit of whether the
13 patients take it or not.

14 As I have testified today, the complementarity
15 is primarily the first few days using the drug. Once the
16 steroid has had enough time to work, then the benefit of
17 combining them pharmacologically would be relatively modest.

18 Q. So maybe I can refresh your memory. May I turn you
19 to your deposition? It's Tab 1.

20 A. Sure. Okay.

21 Q. Please turn to 219, page 219, line 21.

22 MR. KLEIN: Objection. That is not inconsistent
23 with the testimony.

24 THE COURT: All right. Well, I overrule the
25 objection. You may try to impeach him with this if you

Schleimer - cross

1 wish.

2 BY MR. VARUGHESE:

3 Q. Dr. Schleimer, during your deposition you were asked:

4 "Question: So the gains of combining them into
5 a single fixed dose formulation is modest?"

6 "Answer: Yes."

7 Correct?

8 A. Yes.

9 Q. Is your opinion changing here today?

10 A. I'm giving you more information about my opinion,
11 which is that the superiority of the combination would be
12 anticipated to be transient during the first few days of the
13 use of the drug.

14 MR. VARUGHESE: You can put that away. Thank
15 you. I want to turn to the Cramer reference that you
16 testified about.

17 Can we go to DDX-4.39, please?

18 BY MR. VARUGHESE:

19 Q. And this is that Cramer reference; correct?

20 A. Yes.

21 Q. And this is the slide in your demonstratives that we
22 just discussed?

23 A. Yes.

24 Q. And is it your position that this reference renders
25 the invention of this case obvious?

1 A. I think this reference reports the essence of the
2 invention.

3 Q. So would it or would it not have rendered the
4 invention obvious to a person of ordinary skill in the art?

5 A. I'm not a patent lawyer, but I think it would render
6 it obvious by having stated it five years in advance of the
7 priority date.

8 Q. Stated what?

9 A. Stated the invention.

10 Q. Okay. Let's explore that in a bit. This published
11 in 1997; correct?

12 A. Yes.

13 Q. And the date of invention in this case is 2002?

14 A. Yes.

15 Q. So since this was published in 1997, are you aware of
16 the Nielsen and Howarth review articles that published
17 regarding antihistamine and steroid coadministration?

18 A. Yes.

19 Q. And is it true that Nielsen, a review article
20 exploring the great weight of data that was available
21 concluded there was no benefit to adding an antihistamine to
22 a corticosteroid?

23 A. Yes. I think those two articles were contrary
24 articles and people who wrote the ARIA guidelines as well as
25 practicing physicians disagreed with those two groups.

Schleimer - cross

1 Q. Now, there's no clinical data in the Cramer reference
2 to suggest that Nielsen is wrong; is that right?

3 A. I'm not aware of any clinical data. I've read
4 through this and I didn't see any.

5 Q. And a POSA would have read Nielsen after the POSA
6 would have read Cramer; is that correct?

7 A. I think Nielsen was one; right?

8 Q. Yes.

9 A. Yes.

10 Q. Okay. So the POSA's thinking would have advanced as
11 the years went on?

12 A. Hopefully.

13 Q. Okay. Now, this Cramer reference is actually a
14 patent application.

15 Do you understand that?

16 A. Yes.

17 Q. And it belonged to Procter & Gamble?

18 A. The application came from Procter & Gamble.

19 Q. You're familiar with Procter & Gamble?

20 A. Somewhat.

21 Q. Sophisticated pharmaceutical company?

22 A. Yes.

23 Q. But Procter & Gamble never marketed an azelastine
24 fluticasone combination product; isn't that correct?

25 A. As far as I know.

Schleimer - cross

1 Q. And, in fact, Procter & Gamble never marketed a
2 combination product with any antihistamine or
3 corticosteroid?

4 A. Not to my knowledge.

5 Q. Okay. Now, turning back to Cramer, there's no
6 examples in Cramer of specifically adding fluticasone to
7 azelastine in a single formulation; isn't that correct?

8 A. I don't recall, but I think that's correct, although
9 both of those drugs were mentioned as leading candidates in
10 the combination.

11 Q. And you understand during prosecution of the
12 patents-in-suit here, the Examiner issued those patents or
13 approved them over this Cramer reference after having
14 considered it?

15 A. I would be disappointed if that were not true, but I
16 didn't read all of the documents outlining that decision.

17 Q. You didn't read the prosecution history of the
18 patents-in-suit?

19 A. I did. I got a folder, but I don't remember
20 discussion beyond a mention of Cramer.

21 Q. I'm going to try to simplify my question. So the
22 Patent Examiner at the United States Patent and Trademark
23 Office, in prosecuting the patents-in-suit here, considered
24 and discussed Cramer and issued the patents-in-suit despite
25 Cramer; isn't that correct?

Schleimer - cross

1 A. I will take your word for it.

2 Q. Okay. Thanks.

3 And, Dr. Schleimer, you also understand that the
4 law presumes issued patents to be valid?

5 A. You're the first person to tell me that, but I'm
6 pleased to hear it.

7 Q. Okay. Dr. Schleimer, do you know the state of this
8 Cramer application, what came of it?

9 A. I don't.

10 Q. Do you understand that it never issued as a patent?

11 A. That much I know.

12 Q. Do you understand that Procter & Gamble actually
13 abandoned it in one?

14 A. That would be a reasonable explanation.

15 Q. And a POSA would have been aware that Procter &
16 Gamble abandoned this application; right? That abandonment
17 would be in the file history in Cramer?

18 A. Possibly, yes.

19 Q. So given that event, a POSA would understand that a
20 sophisticated pharmaceutical company like Procter & Gamble
21 took the effort to file a patent application and put forth
22 the disclosures that you are relying on with an abandonment
23 and never formulated a product?

24 A. Yes, but a POSA would understand that P&G hasn't
25 really been heavily involved in the respiratory area, and

1 they would also probably understand that there were some
2 patents in the literature that precluded their making the
3 particular combination we're talking about.

4 Q. So despite that knowledge, it's your position that a
5 POSA knowing that P&G abandoned this would nevertheless have
6 proceeded to be motivated to put azelastine and fluticasone
7 in a single formulation?

8 A. I think there would be the motivation to do it, but
9 as I said, there were other patents that made it from a
10 business sense very difficult.

11 Q. And you just testified that a POSA would know that
12 Procter & Gamble -- and I'm going to paraphrase and you can
13 correct me -- that Procter & Gamble didn't have a big
14 footprint in the respiratory area. Isn't that what you just
15 said?

16 A. Yes, I think so.

17 Q. Yet you think that a POSA would rely on this in
18 rendering this invention obvious though, having this
19 knowledge?

20 A. I just think this describes the invention very well.
21 Why P&G didn't develop it, that's pure speculation.

22 Q. And given your testimony, a POSA would think that P&G
23 is inexperienced in respiratory, but your obviousness
24 position is that a POSA would run to this reference and
25 would have easily went out and made a similar invention.

1 Isn't that what you are saying?

2 A. I just said it's not that easy at that time because
3 of patents that made it difficult, other patents.

4 Q. I'm going to turn to DDX-4.41 in your demonstratives.
5 This is the other reference you discussed today, Segal;
6 right?

7 A. Yes.

8 Q. And is it your opinion that the teachings of the
9 Segal reference render Cipla's patents obvious?

10 A. I think that Segal had the same basic idea to combine
11 and intranasal anti-inflammatory steroid with a rapidly
12 acting drug and they mentioned both fluticasone and
13 azelastine.

14 Q. This is another patent application; right?

15 A. Yes.

16 Q. And it belonged to Warner-Lambert?

17 A. Yes.

18 Q. Would you agree that Warner-Lambert is a
19 sophisticated pharmaceutical company?

20 A. Yes.

21 Q. What do you think a POSA would have thought of
22 Warner-Lambert's respiratory prowess?

23 A. That's a good question. I'm not aware of any big
24 drugs they had on the market, but they may have made an
25 antihistamine or two. I don't know.

Schleimer - cross

1 Q. And then they eventually merged with Pfizer; is that
2 correct?

3 A. If you say so.

4 Q. You consulted for Pfizer; right?

5 A. Yes.

6 Q. How long have you been consulting for Pfizer?

7 A. Oh, off and on, I visited them a few times over the
8 years.

9 Q. All right. To your knowledge, did Warner-Lambert
10 ever come to market with an antihistamine corticosteroid
11 combination?

12 A. No.

13 Q. Let's turn to the reference itself and the disclosure
14 that you put up here.

15 So this reference, you can correct me if I'm
16 wrong, says, a combination of a topical anti-inflammatory
17 agent and a therapeutically effective amount, and we'll get
18 back to the at least -- at least one agent suitable for
19 topical nasal administration from this following list; is
20 that right?

21 A. Yes.

22 Q. Okay. And I counted. This is eight different
23 therapeutic categories of drugs.

24 A. Yes.

25 Q. And do you have any idea how many specific agents

Schleimer - cross

1 will be encompassed within those eight categories?

2 A. Oh, I saw your opening slide and it's a large number.

3 Q. A fairly large number, yet it's your position that a
4 POSA would have went to fluticasone and azelastine looking
5 at that fairly large number; is that right?

6 A. I think that Sheldon Spector in the paper that I
7 presented really went right to the heart of it, basically
8 putting his finger on the anti-inflammatory steroid and the
9 antihistamine, and Bill Berger did the same thing in his
10 article. He said, you can combine azelastine with an
11 intranasal steroid. You should try it, essentially, in his
12 review.

13 Q. So certainly I saw your slides on Berger and Spector,
14 but I'm talking about people right now.

15 Is it your position that a POSA reviewing
16 Segal would have been motivated to go put azelastine and
17 fluticasone in a fixed dose combination product?

18 A. It's my position that Segal contributes to the
19 evidence that people years before the priority date were
20 thinking about the essence of this combination, putting an
21 intranasal steroid with a rapidly acting drug.

22 Q. So looking at the two therapeutic categories that you
23 picked here, anti-inflammatory agents, I count six.
24 Antihistamines, I count nine. Doing some simple math, I
25 come up with 54 combinations.

1 Do you agree with that?

2 A. That sounds right, six times nine.

3 Q. And azelastine-fluticasone combination would be one
4 among those 54; right?

5 A. That is correct.

6 Q. And you think that would have been obvious out of
7 that group?

8 A. Yes, I think it would have been obvious to use an
9 intranasal steroid as the cornerstone of your combination
10 since those are by far the most effective drugs, and then
11 you could have added some of those and gotten possibly a
12 better drug, but as I mentioned, only the antihistamine
13 fully inhibited the early phase response.

14 Q. Now, Segal doesn't go on to discuss any
15 particularities of azelastine or fluticasone; is that right?

16 A. I think that's correct.

17 Q. In fact, unlike Cramer, which provided some samples
18 of other drugs, Segal doesn't even provide one sample; isn't
19 that correct?

20 A. Yes. I think Segal is less specific.

21 Q. Do you know the fate of Segal? I'm sorry. Not the
22 inventor.

23 A. I was about to be sad. The Segal application I don't
24 think was ever approved.

25 Q. Okay.

Schleimer - cross

1 A. Maybe not even filed. I don't know.

2 Q. And do you understand it was actually abandoned by
3 Warner-Lambert in 2000?

4 A. I'm prepared to believe that.

5 Q. And a POSA would know that abandonment?

6 A. Possibly. The idea would live on.

7 Q. Now, we just discussed Cramer and Segal, but it's
8 your opinion that these two references aren't even the
9 closest prior art; is that correct?

10 A. That's correct.

11 Q. In your view, Dr. Accetta's prior conjunctive use was
12 the closest prior art?

13 A. Yes. Physicians that were already prescribing both
14 intranasal drugs to the same patient at the same time, and
15 essentially those drugs were being mixed in the nose of the
16 patients who had both prescriptions, monotherapies.

17 Q. So, Dr. Schleimer, is it your opinion that a nasal
18 antihistamine is better than an oral antihistamine?

19 A. That's a difficult question to answer. I think
20 both -- if using the right drugs, both are effective against
21 the early phase.

22 Q. So are they equal?

23 A. Well, I have not seen a lot of head-to-head studies.
24 They seem to be largely equal, but, of course, with the
25 intranasal antihistamine, since it's intranasal, it gives

Schleimer - cross

1 one an opportunity to combine it with the intranasal
2 steroid, which one does not have in a formulation sense with
3 the oral antihistamine.

4 Q. So is it your opinion in this case that a POSA as of
5 2002 would have preferred a nasal antihistamine?

6 A. You know, some patients don't like to take intranasal
7 drugs, and the oral antihistamines are very effective, and
8 as Dr. Wedner testified, they have certain benefits against
9 the diathesis, what he called the allergic diathesis.

10 Many patients, they don't just have
11 allergic rhinitis. They have problems in their eyes, they
12 have problems with their skin. And so I would think it
13 would vary in patient to patient whether an oral
14 antihistamine or an intranasal was the preferred.

15 Q. And so you think a POSA would have preferred
16 intranasal?

17 A. I think I answered that question.

18 Q. It was a lengthy answer, and you've taken some firm
19 positions in your demonstrative and I'm trying to test those
20 theories. So are they equal? Would a POSA in 2002 have
21 been drawn to an oral one or an intranasal one?

22 A. I think it would depend on the physician and the
23 patient.

24 Q. Well, we're talking about a POSA.

25 A. Well, if we're talking about a POSA who is trying to

Schleimer - cross

1 make an improved drug as a combination, then the only one
2 that you could combine with the intranasal steroid and a
3 single formulation would be the intranasal antihistamine.

4 Q. Did you have a preference for intranasal or oral at
5 that time?

6 A. As you know, I'm not a treating physician. I have
7 used these drugs myself since I have allergic rhinitis and I
8 prefer intranasal, but many patients don't like intranasal
9 drugs.

10 Q. Can we go to the '620 patent, please. Let's go to
11 Example 3. Just a few more questions, Dr. Schleimer.

12 You testified earlier that the patents provide
13 no dosing information or guidelines of patents. Is that
14 fair to say? Is that a fair representation of your
15 testimony?

16 A. Yes.

17 Q. Now, I'm directing you to the '620 patent
18 specification, Example 3. Can we highlight the azelastine
19 on the bottom?

20 Do you see that this is a nasal spray with
21 azelastine and fluticasone, and the asterisk says that each
22 spray delivers 140 micrograms of azelastine and 50
23 micrograms of fluticasone?

24 A. Yes, and sorry. This is excerpted from --

25 Q. The patents-in-suit.

1 A. The '620 patent?

2 Q. Correct.

3 A. Okay. Yes, I see that.

4 Q. And is it your opinion that an M.D. according to your
5 POSA definition would understand how to dose or dose titrate
6 based on that disclosure?

7 A. No. I think an M.D. that treats allergic rhinitis
8 would look at those and know that that is the dose per spray
9 of the monotherapies.

10 Q. Wouldn't an M.D. looking at that know that that could
11 provide a starting point, identify the effective dose?

12 A. As I said, I mean, they would know that Astelin uses
13 137 in the U.S., 140 micrograms per spray, and they would
14 know that fluticasone uses 50 micrograms per spray. But
15 they would not necessarily know how to dose the combination.

16 Q. This is a combination here disclosed, isn't it?

17 A. Yes.

18 Q. Okay. And describing the combination, the inventors
19 are telling the world that their combination has per spray
20 140 micrograms of azelastine and 50 micrograms of
21 fluticasone.

22 Is it your opinion that a POSA under your
23 definition wouldn't know how to arrive at the effective dose
24 based on this disclosure?

25 A. Well, this is helpful, but it would be an unknown

Schleimer - cross

1 number of sprays. For instance, per day.

2 Q. I'd like a yes-or-no answer to that question. Is it
3 yes or no? Would a POSA reviewing that disclosure know how
4 to arrive at the effective dose by practicing dose
5 titration?

6 A. It's not a yes-or-no answer. I'm sorry. A POSA
7 would know that these were the already approved quantities
8 of drug per spray for those two monotherapies.

9 Q. So you won't give me a yes-or-no answer to that?

10 A. No.

11 MR. VARUGHESE: Nothing further, your Honor.

12 THE COURT: Thank you.

13 Redirect?

14 MR. KLEIN: No redirect, your Honor. I managed
15 to locate my demonstratives. They were on the Elmo.

16 THE COURT: Oh, okay.

17 MR. KLEIN: So I will hand those up.

18 THE COURT: Thank you very much.

19 You may step down.

20 THE WITNESS: Thank you.

21 (Witness excused.)

22 (Mr. Klein handed demonstratives to the Court.)

23 THE COURT: We're going to take a short recess
24 before the next witness.

25 (Brief recess taken.)

Donovan - direct

1 THE COURT: All right. Have a seat.

2 What is next?

3 MR. LOMBARDI: Next for Apotex is Dr. Maureen
4 Donovan.

5 THE COURT: Okay.

6 MR. LOMBARDI: And, Your Honor, I believe her
7 materials we put up during the break. And we have some
8 yourself and the clerk.

9 THE COURT: Okay.

10 A VOICE: May I approach?

11 THE COURT: Yes.

12 (Documents passed forward.)

13 ... MAUREEN DONOVAN, having been first duly
14 sworn, was examined and testified as follows ...

15 THE COURT: Welcome, Dr. Donovan. Good evening.
16 You may proceed, Mr. Lombardi.

17 MR. LOMBARDI: Thank you, Your Honor.

18 DIRECT EXAMINATION

19 BY MR. LOMBARDI:

20 Q. Dr. Donovan, would you please state your name for the
21 record?

22 A. Maureen Donovan.

23 Q. And just generally before we get into all the
24 details, what are you here to testify about?

25 A. I'm here to testify about nasal formulation and nasal

Donovan - direct

1 drug delivery.

2 Q. We're going to talk about your background. You
3 brought your CV to court?

4 A. Yes, I have.

5 Q. Let's put that up. That is DTX-293, which I have put
6 on slide DDX-5.01. That your CV; is that correct?

7 A. That's the first couple of pages, yes.

8 Q. Would you describe for us briefly your educational
9 background?

10 A. I have a bachelor's degree in Pharmacy from the
11 University of Minnesota.

12 After completion of that degree, I went to the
13 University of Michigan, completed a Ph.D. in Pharmaceutics
14 in 1989.

15 And after that I joined the faculty of the
16 University of Iowa.

17 Q. And you studied Pharmacy. Just describe generally
18 what it means at least in your case to have studied
19 pharmacy?

20 A. Well, as in my undergraduate preparation, I studied
21 the area of pharmacy. When I graduated, I was eligible to
22 be licensed and practice as a pharmacist.

23 I was licensed for a period of time and did
24 practice pharmacy; and at the time, I decided that I liked
25 science and so I pursued a graduate degree.

Donovan - direct

1 Q. Is part of your education in the formulation arts as
2 well?

3 A. Correct. Yes.

4 Q. So what did you do after receiving your Ph.D. in
5 Pharmacy?

6 A. I joined the faculty of the University of Iowa.

7 Q. And what year was that?

8 A. 1989.

9 Q. And what you have done since then?

10 A. I have taught. I have done research. I have done a
11 number of service activities, served at all the academic
12 levels that are typical of a university faculty position;
13 and I now serve as an Associate Dean.

14 Q. And just to be clear, you have been at Iowa since
15 1989?

16 A. I have been at Iowa since 1989.

17 Q. And always with the College of Pharmacy?

18 A. Yes, sir.

19 Q. And you have held a variety of administrative roles
20 at the university?

21 A. Yes, I have.

22 Q. What kind of work have you done within the field of
23 pharmacy since you have been at Iowa?

24 A. Most of my research is directed at nasal absorption
25 and through the interface between formulation and absorption

Donovan - direct

1 effects. The primary focus of my research for the years
2 since even before 1989 has been in the area of nasal drug
3 absorption and nasal formulation effects on nasal drug
4 absorption.

5 Q. In the course of that time, have you done work on
6 actually formulating drugs?

7 A. Yes, I have.

8 Q. And how about drugs that are nasal drugs,
9 administered nasally?

10 A. I would venture that nearly every experimental system
11 that we entertained involves formulating something that
12 would be intended to investigate as a nasal delivery system
13 or at least nasal absorption.

14 Q. In addition to your teaching duties, have you done
15 consulting work?

16 A. Yes, I have.

17 Q. Can you describe generally the type of consulting
18 work you have done over that period of time?

19 A. I have been a consultant to the pharmaceutical
20 industry. Primarily, I am called upon to provide general
21 information about nasal delivery or at times I'm called on
22 to ask specific things about a nasal formulation or a
23 delivery project that a company is either considering or
24 is pursuing.

25 I have also given expert testimony for various

Donovan - direct

1 drug companies.

2 Q. Let me put the expert testimony aside for a moment
3 and ask you about the other consulting work you do.

4 Typically, what kinds of things are you
5 consulted on outside of expert work you might do in
6 association with litigation?

7 A. Most frequently, I am asked to come in and both teach
8 about nasal absorption and nasal formulation and properties
9 of nasal formulations or drug delivery systems.

10 I have also been called upon for other areas of
11 routes of administration that I have an interest in to give
12 presentations in those areas also.

13 There are times where a company has a specific
14 question and wants a more focused visit about a specific
15 problem that they would like to solve. And there are other
16 situations where in a more general sense we have done
17 experimental work for companies also.

18 Q. Okay. And the companies you consult with, can you
19 characterize for us whether they're for a brand companies,
20 generic companies, a mix?

21 A. Most of the formulation development type consulting
22 work is in the branded space and dealing with -- it's in a
23 variety of new chemical entities or currently used and known
24 and approved molecules.

25 Q. And you have also, you said you did consulting work

Donovan - direct

1 in the course of litigation. Have you been accepted as an
2 expert on nasal formulations in litigation before?

3 A. Yes, I have.

4 Q. You present at academic conferences?

5 A. Yes, I do.

6 Q. And on nasal formulation issues?

7 A. Quite frequently, yes.

8 Q. And have you written articles about scientific
9 issues, formulation issues?

10 A. Yes, I have a number of publications probably in the
11 order of 40 to 50 publications in the area of nasal drug
12 delivery.

13 Q. Can characterize to us to what extent those
14 publications involve nasal formulation issues?

15 A. They either involve nasal formulation or nasal
16 absorption issues, primarily.

17 Q. All of them?

18 A. There is a few that aren't focused on nasal, but the
19 vast majority is in the area of nasal delivery, nasal
20 absorption.

21 Q. Now, apart from the articles that you have written,
22 have you worked on things called abstracts?

23 A. Yes. I published over 80 abstracts. I combined 80
24 abstracts, maybe another 40 presentations at national
25 meetings or other venues.

Donovan - direct

1 Q. When you say an abstract, just so we have it on the
2 record, what are you referring to?

3 A. Usually, it is the short written version of a
4 presentation that is going to be given, whether it is a
5 poster presentation or a podium presentation or a
6 presentation in a seminar format.

7 Q. And to what extent do those abstracts involve nasal
8 formulation or issues related to nasal formulation?

9 A. Many of them. The vast majority of them are still
10 addressing nasal delivery nasal absorption.

11 Q. Doctor, have you formulated nasal sprays yourself?

12 A. Yes, I have.

13 Q. Have you consulted on the formulation of nasal
14 sprays?

15 A. Yes, I have.

16 Q. Have you testified before on the formulation of nasal
17 sprays?

18 A. Yes, I have.

19 Q. Have you written articles on the nasal administration
20 of drugs?

21 A. Yes, I have.

22 MR. LOMBARDI: Your Honor, I offer Dr. Donovan
23 as an expert in the formulation of pharmaceuticals,
24 including specifically nasal formulations.

25 THE COURT: Any objection?

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1 MS. EVERETT: No objection.

2 THE COURT: She is so recognized.

3 BY MR. LOMBARDI:

4 Q. Dr. Donovan, let's move to your opinions in the case.
5 And before we get into everything, I just want to give the
6 Court an idea of where we're going.

7 Can you provide for the Court a summary of the
8 opinions you are going to express here?

9 A. Sure. The brief summary is that I have found that
10 I believe a POSA formulator co-formulating a fluticasone
11 propionate/azelastine hydrochloride nasal spray would have
12 started by working on the Flonase or starting with using the
13 Flonase and Astelin products at the time of 2002.

14 And the claimed combinations of both fluticasone
15 propionate and azelastine hydrochloride in that nasal spray
16 are obvious.

17 Q. Okay. And, Doctor, you are obviously not a lawyer;
18 is that correct?

19 A. I am not a lawyer.

20 Q. And have you been given some type of instruction on
21 the type of analysis that needs to be done in this type of
22 case; correct?

23 A. Yes, I have.

24 Q. Can you let the Court know what is the analysis in
25 a general sense that we're going to be going through here

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1 today?

2 A. Okay. What I did regarding this issue was first I
3 needed to identify what I believe the level of ordinary
4 skill in the art of somebody who would be undertaking
5 formulating projects likes this.

6 And then following that, took a look at what was
7 available in the prior art prior to 2002 that would enable
8 that formulator to move forward on a project.

9 And then, after I had identified the prior or
10 most relevant prior art, then I took a look at that prior
11 art and also developed some conclusions about the prior art
12 and used that to assess the differences between the prior
13 art and the claimed inventions.

14 And then, finally, made a determination about
15 whether the claimed inventions were obvious.

16 Q. Okay. And the first thing you talked about there is
17 the level of skill in the art.

18 Have you defined a person of ordinary skill in
19 the art for purposes of your testimony?

20 A. Yes, I have.

21 Q. And let me first ask you, we've put up on the screen
22 the level of skill in the art. You have seen the definition
23 of the person of ordinary skill in the art provided by
24 plaintiffs' formulation expert, Dr. Smyth; is that correct?

25 A. Yes, I have.

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1 Q. Do you consider your definition materially different
2 from his?

3 A. Outside of the extent of experience with direct nasal
4 formulation or sterile product formulation, our descriptions
5 of a POSA are quite close.

6 Q. Okay. And would you tell the Court how you defined
7 the person of ordinary skill in the art for purposes of this
8 case?

9 A. Well, I defined the person that would have the
10 opportunity to have various levels of education combined
11 with experience to put them into a position of being a
12 POSA in the area of nasal formulation.

13 So if it was an individual who had a bachelor's
14 degree in typically areas like chemistry, biology, chemical
15 engineering, pharmaceutical science, or a closely related
16 area, those individuals would need about three to five years
17 of experience in formulation development specifically of
18 nasal dosage forms and be of the ability to operate
19 independently on those formulation activities.

20 If they had higher education, then likely fewer
21 years of experience would be needed.

22 And then regardless of level of education, the
23 individual would have to have a familiarity with
24 pharmaceutical excipients and their uses.

25 Q. Okay. And you said that Dr. Smyth's definition was

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1 slightly different. If you were to apply Dr. Smyth's
2 definition to your analysis, would it change the results for
3 you?

4 A. No.

5 Q. All right. Doctor, what is the date, the critical
6 date for purposes of your obviousness inquiry?

7 A. I have been told the critical date is June 2002.

8 Q. Let's move to your analysis. Where did your analysis
9 begin in this case?

10 A. My analysis began with the commercial products that
11 were already available in the marketplace, and the
12 information that could be obtained from those products.

13 Q. Okay. Let me step back just a second. When a
14 formulator gets an assignment to do a formulation, are there
15 a variety of ways that you are given that kind of work?

16 A. Oh, certainly. And, you know, if you are working
17 with a team of clinicians or have interactions with
18 clinicians, oftentimes they will pose ideas or provide
19 information for something that they would like done, if you
20 are working in the industry, as oftentimes there is a
21 similar proposition where somebody assigns an activity for
22 you to work on.

23 There are times where POSA formulators develop
24 their own ideas about formulations and pursues those.

25 Q. And just for the record, you say "POSA." To the

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1 extent you say "POSA," that means person of ordinary skill
2 in the art; right?

3 A. Yes.

4 Q. Thank you. So in this particular case, you have
5 listened to various experts talk about azelastine
6 hydrochloride and fluticasone propionate. Where did your
7 analysis begin?

8 A. It began, most of it, the initial analysis began by
9 looking at the commercially available products containing
10 fluticasone propionate, containing azelastine hydrochloride
11 that were available as nasal sprays.

12 Q. Why begin with the commercially available products?

13 A. Because, as a formulator, there are, there is
14 information that can be gained from evaluating a currently
15 available product. And oftentimes, that will lead you in
16 your starting direction for formulation.

17 Q. And what were the two products that you are referring
18 to?

19 A. There were two products in the marketplace: one
20 containing fluticasone propionate, the brand name known as
21 Flonase at the time, and then another nasal spray product
22 that was containing azelastine hydrochloride that was known
23 as Astelin.

24 Q. Okay. And let's start with Flonase. What was the
25 information you found that would be available to the person

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1 of ordinary skill in the art concerning Flonase at the time
2 of the critical date?

3 A. Well, one of the most condensed forms of information
4 about the formulation of a commercial product is the FDA
5 approved label, and so that's often the first place I go to
6 look for formulation information.

7 Q. All right. And did you bring that label with you
8 here today?

9 A. I did.

10 Q. All right. Let's go to the next slide, and this is
11 DTX-33, and what's displayed on the slide is page 2 and it's
12 DDX-5.05.

13 Can you describe for the Court what's
14 depicted here?

15 A. Yes. What's depicted on the left that's denoted
16 Flonase label is the beginning portion of the FDA label for
17 the product Flonase.

18 Q. And this is information that comes with the drug; is
19 that correct?

20 A. Yes. It's approved by the FDA.

21 Q. All right. And so just as a starting point, does the
22 label provide some basic information about the nature of
23 fluticasone propionate?

24 A. Yes. We can see already that its label provides the
25 chemical structure of the drug, provides the name. It

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1 provides information about the actual chemical name of the
2 drug substance. It tells us what the dosage form is
3 frequently, and this one in this case, it's denoted as a
4 nasal spray.

5 Other descriptions of the formulation are
6 contained in the label, and of specific interest to a
7 formulator are the list of ingredients contained in the
8 formulation are also part of the label.

9 Q. Okay. And so for right now let's stick with
10 fluticasone propionate. You said it's a nasal spray. Is
11 there other information provided about the nature of how
12 fluticasone propionate is formulated?

13 A. Yes. Specifically, they do, the label describes this
14 particular product as a suspension, aqueous suspension.

15 Q. All right. We've heard something about that so far,
16 but from the standpoint of a formulator, what is a
17 suspension?

18 A. A suspension is a dosage form where there is
19 undissolved material, and in this case undissolved drug in
20 equilibrium with dissolved drug and likely having other
21 components to make that formulation something that is useful
22 for application to a human or an animal.

23 Q. Okay. Now, you have had a chance to review the
24 Flonase label; is that correct?

25 A. Yes.

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1 Q. Have we brought a chart to court to help make your
2 testimony proceed more smoothly?

3 A. Yes. To simplify from reading the tiny font for
4 everyone, we've put together a list of, or a chart
5 containing the ingredients because that's going to be the
6 focus of the formulation activity.

7 Q. Okay. Let me go to the next part. This is DDX-5.06,
8 and is that the chart you just referred to?

9 A. Yes, it is.

10 Q. And just describe generally, and we'll get into the
11 specifics in a moment, what is depicted on the chart?

12 A. Okay. So the chart here under the column that's
13 labeled Flonase are the ingredients that are listed in the
14 label for the product Flonase. And to the left of that,
15 I've added a column that describes the general or most
16 likely purpose for each of those ingredients contained in
17 the formulation.

18 Q. All right. So let's start at the top. The
19 ingredient you've already identified is fluticasone
20 propionate; is that correct?

21 A. That's correct.

22 Q. What is the further information that you provide
23 there in the parenthetical?

24 A. Well, in a number of different ways to help us in the
25 future, there's information about the amount of drug

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1 delivered per spray from the Flonase bottle. So
2 50 micrograms, and if you do the equivalents calculations,
3 0.05 milligrams per spray, or if we do that in terms of a
4 percent concentration in the vehicle, 0.05 percent or
5 0.5 milligrams per ml.

6 Q. Okay. And you did some calculations to come to some
7 of those numbers; is that right?

8 A. Yes, I did.

9 Q. And which is the number that was actually given in
10 the label so the record is clear?

11 A. The label tells us that each spray from the dose, the
12 delivery system contains 50 micrograms of micronized
13 fluticasone propionate in a hundred milligram spray.

14 Q. All right. Let's look at particle size. When we're
15 talking about particle size in Flonase, what is the particle
16 size that we're talking about?

17 A. The label itself details that it's microfine.
18 Fluticasone propionate. And that microfine term tells the
19 formulator that it's a size controlled, or a particle size
20 controlled solid, and the microfine indicates that it's less
21 than ten microns, the particles are less than ten microns in
22 size.

23 Q. Okay. Would a person of skill in the art understand
24 what microfine means?

25 A. Yes.

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1 Q. Would a person of skill in the art understand how to
2 make microfine particles?

3 A. They would understand either how to make them
4 themselves or they would understand how to find individuals
5 or companies that will help them with micronization.

6 Q. Okay. The next category is vehicle. Before we talk
7 about what the vehicle is, what is a vehicle generally in a
8 pharmaceutical formulation?

9 A. Well, vehicle is sort of the media in which
10 everything is placed to allow you to then deliver it in the
11 way you want. So in the case of a nasal spray, the vehicle
12 is the fluid portion of the formulation that allows you to
13 contain the drug in other materials and then is a portion of
14 what is administered.

15 Q. And in this case, Flonase, what's the vehicle?

16 A. The vehicle is water.

17 Q. Is that an unusual vehicle for a nasal spray?

18 A. It's a very common and preferred vehicle.

19 Q. All right. Let's go to preservatives. And, again,
20 what is a preservative generally, first?

21 A. A preservative is something that gets added to a
22 formulation to increase its stability or maintain its
23 properties, and in this case the preservatives that are
24 identified here are antimicrobial preservatives. And the
25 reason that we put antimicrobial preservatives into nasal

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1 sprays is because there's a high likelihood for bacterial
2 contamination in the containers that we oftentimes provide
3 nasal sprays with a month's worth of dose or so, a week's
4 worth of dose, what we in formulation call a multidose vial.
5 And so we don't want bacteria to grow between the time of
6 administration, so we add materials that are known to limit
7 bacterial growth or to kill bacteria.

8 And the two items, benzalkonium chloride
9 and phenylethyl alcohol, are both known preservatives that
10 act as antibacterial preservatives.

11 Q. And somewhere in your answer you made reference to
12 something called antimicrobial. Can you define that?

13 A. Right. Antimicrobial, again, we're trying to reduce
14 microbial growth, if there was any contamination of the
15 spray system following use.

16 Q. You mentioned benzalkonium chloride, which is number
17 one under preservatives, and there's an amount there as
18 well; is that correct?

19 A. Yes.

20 Q. Is that something that would have been known to a
21 person of skill in the art as of 2002?

22 A. Yes. Benzalkonium chloride is a very commonly used
23 antimicrobial preservative. And that's a very commonly used
24 concentration range for that activity.

25 Q. And how about phenylethyl alcohol? Also you have

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1 0.25 percent. That's the amount; is that correct?

2 A. That's correct.

3 Q. Is that something a person of skill in the art would
4 have been familiar with as of the critical date?

5 A. Yes. Similarly, phenylethyl alcohol is used as an
6 antimicrobial preservative in a number of formulations, and
7 again this concentration used in the Flonase product is a
8 typical concentration for antimicrobial preservation.

9 Q. Okay. Surfactants is the next category. What is a
10 surfactant generally?

11 A. A surfactant is an agent that has both water liking
12 and water hating properties, or we turn that into
13 hydrophilic and hydrophobic properties. And in the case of
14 a suspension formulation where the vehicle is water, one of
15 the reasons that we have that suspension is likely that the
16 material we've added may not have great water solubility,
17 which means it may have hydrophobic tendencies.

18 And so what we're trying to do to improve
19 the quality of the suspension is allow the solid material to
20 not stay collected as a big lump, and we want to be able to
21 disperse the particles of that solid, so we use a surfactant
22 and its hydrophobic character to interact with the surfaces
23 of those particles, and then the hydrophilic particle that's
24 part of the same molecule interacts with the water system.
25 And it allows those particles then to disperse within and

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1 have a much lower tendency to aggregate back together again
2 in the -- within the system upon rest. So we call that a
3 wetting agent in this case.

4 Q. How often are surfactants used in the world of
5 pharmaceutical formulations?

6 A. They are used quite frequently in pharmaceuticals.
7 They are used very frequently in food products also.

8 Q. All right. And the surfactant that you have listed
9 here as polysorbate 80, can you identify that for the Court?

10 A. Yes. Polysorbate 80, it's a very common surfactant
11 used in both pharmaceutical products and food products.

12 Q. All right. Let's go to the next category, thickening
13 agents. What does that refer to?

14 A. A thickening agent makes the vehicle thicker, and
15 there are reasons why for nasal delivery that we might want
16 a thicker vehicle. There's certainly reasons in a
17 suspension you like a thicker vehicle.

18 So one of the characteristics of
19 suspensions frequently is again the particles have a
20 tendency to settle. They have a different density than the
21 water does. And as a result, they group together on the
22 bottom of the container. And we like perhaps to make that
23 not happen as much or happen in a different fashion than in
24 water alone, and so they'll add a thickening agent to slow
25 that process or to alter that process somehow.

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1 In nasal formulations in addition, we have a
2 tendency to like to add thickening agents under the
3 presumption that having a slightly thicker than water
4 vehicle sprayed into the nose or dropped into the nose,
5 that it will stay there longer. It won't drain out the back
6 of your throat or out of the tip of your nostrils as
7 quickly.

8 Q. Okay. And a thickening agent, are thickening agents
9 frequently used in nasal formulations?

10 A. Quite frequently used in nasal formulations, yes.

11 Q. All right. And the thickening agent that you have
12 listed here for the Flonase label is microcrystalline
13 cellulose/carboxymethyl cellulose sodium. Easy for me to
14 say, Doctor.

15 A. Yes. And probably easier for me to say.

16 Q. All right.

17 A. I've also abbreviated it so it's easier for everyone.

18 Q. So we're going to refer to it as MCC/CMC?

19 A. Yes, we are.

20 Q. Thank you. And what is MCC/CMC?

21 A. It's a combination of two cellulosic materials. It's
22 very commonly used as a thickening agent in the
23 pharmaceutical industry. On the second term in parentheses
24 in the last line called Avicel tells us that it's actually
25 commercially available as a combination product or a family

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1 of combination products because it is used frequently as a
2 thickening material in the pharmaceutical -- in
3 pharmaceuticals.

4 Q. And so what is Avicel?

5 A. Avicel is again a brand name for microcrystalline
6 cellulose/carboxymethyl cellulose sodium material.

7 Q. Okay. And let's go to the next categories. It says
8 tonicity adjuster. First, what is tonicity?

9 A. Tonicity is a balance. You can look at it as a
10 balance of water concentration across the biological
11 membrane, or it's more easily thought of as a balance of
12 solute concentrations on the, on either side of a biological
13 membrane.

14 And we're not talking specific
15 concentrations of each material. It's total, the total
16 number of solutes dissolved on the outside of a membrane and
17 the total number of solutes dissolved on the inside of the
18 membrane.

19 And typically we like to balance that to a
20 degree because we don't want water to be leaving the inside
21 of a cell to go out into the environment to try to dilute
22 out an environment that has many, many more solute molecules
23 dissolved, or in comparison, if there are not very many
24 solute molecules on the outside of the barrier, that water
25 is going to try to go into the cell and dilute out the

1 solute molecule that are present inside. So we try to
2 balance that to control some of the water redistribution
3 properties.

4 Q. And how common is it for formulators to deal with
5 tonicity?

6 A. It's quite common.

7 Q. How about in nasal formulations?

8 A. Very common in nasal formulations, very common in
9 other formulations that are applied to mucosal surfaces, and
10 we pay a lot of attention to it in materials that are
11 ingested, as each of these ingestibles.

12 Q. All right. So we're talking about a tonicity
13 adjustor here. What is a tonicity adjuster?

14 A. Well, in the simplest sense, a tonicity adjustor is
15 any molecule that will go into solution that will contribute
16 to additional solute molecules in that media.

17 So as we're adjusting tonicity in
18 formulations, we typically pick very water soluble
19 molecules, usually molecules that we believe are going to
20 have little influence on the rest of the formulation, and
21 we're just adding them because we need to add more solute
22 molecules.

23 So the example, the material used in
24 Flonase is dextrose, a very compatible, highly water soluble
25 material. It gets used as a tonicity adjuster in many,

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1 many, many pharmaceutical products.

2 Q. Is it -- is there a way to measure tonicity?

3 A. Yes.

4 Q. And what is the way -- what are the units in which
5 tonicity is measured?

6 A. The units are typically expressed as milliosmoles, or
7 as a concentration, milliosmoles per liter is a frequent
8 measuring system or unit that will see. And really, it's
9 akin to molarity.

10 If we're familiar with a molar
11 concentration, it expresses things in terms of numbers of
12 molecules rather than their weight is the -- perhaps a very
13 general way of describing that.

14 Q. All right. And prior to 2002, did the art provide
15 information about appropriate tonicity for nasal
16 formulations?

17 A. The art could take guidelines regarding appropriate
18 tonicity levels, yes.

19 Q. And did you bring a piece of art?

20 A. I did.

21 Q. That explains that. All right.

22 A. Yes.

23 Q. All right. Let's go to the next slide, which is
24 DDX-5.07, and on that slide is DTX-78 at page 19.

25 Can you first describe for the Court what

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1 the source is that you are referring to here?

2 A. Sure. The source, and what you are seeing here is
3 the front page of a book called, "The Art, Science and
4 Technology of Pharmaceutical Compounding," and the author is
5 Lloyd Allen. And this book is available from a number of
6 edited series now, and it's a book frequently used by
7 compounding pharmacists.

8 We use it in a teaching sense, and it's
9 also used as sort of a basic guideline for formulators
10 because it contains good information about various routes of
11 administration and the requirements for materials to be
12 formulated or used at those routes.

13 Q. Okay. And at page 19 you've called out some
14 information. What have you called out here?

15 A. Well, page 19 is part of the chapter on nasal
16 formulations in this book, and this is a section that
17 describes tonicity adjustment and how that might be taken,
18 undertaken.

19 Q. All right. Does it provide information about the
20 appropriate level of tonicity?

21 A. Yes.

22 Q. And --

23 A. So as underlined in red, tonicity of about 300
24 milliosmoles per liter is oftentimes thought to be about
25 isotonic, so in balance with solute concentration inside of

1 a cell. And that's labeled as ideal in this text. And what
2 Allen also recognizes that for, nasal mucosal administration
3 that ranges between 200 and 600 milliosmoles per liter is
4 acceptable for those formulations.

5 Q. Okay. Typically, how difficult is it for a person of
6 ordinary skill in the art to adjust tonicity in a
7 formulation?

8 A. It's actually quite simple because, again, the
9 general approach to adjusting tonicity when it's identified
10 that one would want to or need to do that is to find a water
11 soluble molecule from usually the commonly used water
12 soluble molecules for adjusting tonicity that are
13 biologically compatible and likely have a low -- would have
14 a low impact on a formulation.

15 Q. Okay. Let's go back to the chart. And I think you
16 referenced this already, but what is the tonicity that's
17 used in the Flonase formulation?

18 A. In Flonase it's dextrose.

19 Q. Is that an unusual tonicity adjuster?

20 A. Again, very common. Used quite frequently,
21 especially in parenterals.

22 Q. All right. Let's go to the next category. It's pH.
23 What's the importance of pH in formulations?

24 A. Well, pH is a measure. In an absolute sense, it's a
25 measure of the hydrogen ion concentration or the hydronium

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1 ion concentration to be more accurate in water. And in
2 general sense, it's a descriptor of the acidity of a
3 particular aqueous system.

4 So numbers less than seven are considered
5 acidic. Numbers greater than seven are considered basic.
6 And so the pH range that's described here for this product
7 is a product specification that you -- during its shelf life
8 that Flonase will maintain a pH between 5 and 7.

9 Q. Do you need a sip of water?

10 A. Thanks.

11 Q. All set?

12 A. Thank you. Yes.

13 Q. And what do formulators do to determine the
14 appropriate pH for a formulation generally?

15 A. There's a number of approaches, but typically using a
16 pH electrode --

17 Q. Take your time.

18 (Pause.)

19 BY MR. LOMBARDI:

20 Q. We'll see if we have a lozenge for you if that would
21 help.

22 A. All right.

23 Q. The question was: What do formulators do to
24 determine the appropriate pH for a formulation?

25 A. They experimentally determine it again, most

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1 frequently with what's designed as a pH meter and an
2 electrode system where they measure a surrogate for pH, and
3 then the equipment itself gives you a reading that you
4 interpret as the pH.

5 Q. All right. And is determining the appropriate pH
6 for a formulation within the level of ordinary skill in the
7 art?

8 A. Absolutely. Done on a daily basis by formulators.

9 Q. Okay. That's Flonase and we're going to move now to
10 Astelin. And where did you look to, for information
11 concerning Astelin?

12 A. Again, in is similar manner to Flonase, Astelin was a
13 product in the marketplace containing Azelastine
14 hydrochloride, so I immediately went to look at the label to
15 see what the contents were.

16 Q. And have we brought the label here today?

17 A. Yes, we did.

18 Q. All right. Let's go to the next slide. It's
19 DDX-5.09, which has an excerpt from DTX-22 at page 6.

20 And can you identify for the Court what
21 DTX-22 is?

22 A. This is again the beginning portion of the FDA label
23 for Astelin.

24 Q. Okay. And start the same way we did before. What
25 does this label tell you? What is the active ingredient in

1 Astelin?

2 A. Azelastine hydrochloride.

3 Q. What does the label tell you generally about
4 azelastine hydrochloride in this formulation?

5 A. Again, it gives us the chemical structure, it gives
6 us the chemical name, some information about some of its
7 chemical properties. The label tells us other things about
8 the concentration of Astelin present in a dose delivered
9 from Astelin spray product.

10 Q. Okay. And so we said that the Flonase was a
11 suspension. What is Astelin?

12 A. Astelin, the azelastine hydrochloride system in
13 Astelin, the dosage form itself is a solution. It's an
14 aqueous solution dosage form.

15 Q. What does it mean to be a solution as opposed to what
16 a suspension is?

17 A. In an aqueous solution, all of the components in that
18 formulation are in solution, in the vehicle.

19 Q. All right. Now, did you review the ingredients and
20 the information on the Astelin label?

21 A. Yes, I did.

22 Q. Have you also used the chart to summarize the
23 information you found there?

24 A. Yes, in a similar format as Flonase.

25 Q. Let's go back to the chart. This is DDX-5.10.

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1 And we start with the active ingredient. With
2 Astelin, you said that is azelastine hydrochloride. What is
3 the information you have in the parenthetical after
4 azelastine hydrochloride?

5 A. As in the same manner as trying to express the
6 fluticasone propionate concentration, a number of different
7 units that we'll see in other pieces of information we'll be
8 referring to.

9 The label says that azelastine hydrochloride is
10 at 0.1 percent concentration in Astelin. And it also tells
11 us that 0.137 milligrams of azelastine hydrochloride are
12 delivered per spray from that spray system.

13 Q. All right. Let's go to the next couple here.

14 Particle size for Astelin, and you say dissolved
15 in solution. Why do you say that?

16 A. Well, its label indicates it's an aqueous solution,
17 formulation; and as a result, there are no particles to be
18 measured. Everything used on a molecular scale is dissolved
19 in the water vehicle.

20 Q. All right. And, again, what is the vehicle here?

21 A. Water.

22 Q. Same as before. Let's go to preservatives. And
23 what are the preservatives that are used in Astelin?

24 A. In Astelin, again, this is a nasal spray. There is a
25 reason to try to include antimicrobial preservatives, to

Donovan - direct

1 limit bacterial contamination. And in the case of Astelin,
2 it contains benzalkonium chloride and EDTA disodium.

3 Q. We talked about benzalkonium chloride. What is EDTA
4 disodium?

5 A. EDTA is ethylenediamine tetraacetic acid, which will
6 come up in a minute, so everybody will understand the term.

7 It is another, it's an antimicrobial preservative
8 adjuvant. It potentially has some antimicrobial
9 preservative activity itself, but it works particularly well
10 in combination with benzalkonium chloride. It also has a
11 couple of other type of formulation roles, so we see it used
12 quite frequently both for its antimicrobial preservative
13 activities and some other activities in many pharmaceutical
14 formulations.

15 Q. Okay. Now, have you looked beyond the Astelin label
16 to other art that is relative to azelastine hydrochloride to
17 see further information about preservatives that can be used
18 with that compound?

19 A. Yes, I did.

20 Q. Where did you look?

21 A. I looked at a patent that describes Astelin or
22 azelastine-containing formulation. And it is frequently
23 referred to, or I refer to it as the Hettche patent or the
24 Astelin patent.

25 Q. Let me go to the next patent, and we'll describe

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1 that. This is slide DDX-5.13. And on the slide is DTX-16
2 at column 2, lines 46 to 68.

3 And you said you refer to it in two ways. One
4 is the Hettche patent. Is that the name of the inventor,
5 H-e-t-t-c-h-e?

6 A. I believe that is the name. That is the name of the
7 inventor, yes.

8 Q. All right. And this patent generally deals with
9 azelastine hydrochloride; is that right?

10 A. Yes.

11 Q. And what is the information at the location that we
12 just called out?

13 A. This excerpt is from a section in the patent that
14 describes the inclusion of preservatives or stabilizers in
15 formulations containing azelastine hydrochloride; and the
16 first recommended stabilizer or preservative in the list is
17 ethylenediamine tetraacetic acid, which EDTA is certainly my
18 preferred way of saying that.

19 And this is a number of other known
20 preservatives and often times gives concentration ranges
21 that would be appropriate. And by the time we get to the
22 end of that paragraph, it gives a more general concentration
23 range that one, a formulator, could use to direct their
24 inclusion at what concentration in a formulation.

25 Q. And what is the concentration that is reported that

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1 is of general use with these preservatives?

2 A. The general concentration is somewhere in a range
3 between 0.002 and 0.05 percent.

4 Q. All right. And we put that on your chart as well?

5 A. Yes, we did.

6 Q. And so there it is adjacent to Astelin patent. It
7 talks about other preservatives in the concentrations you
8 just said; is that correct?

9 A. That is correct.

10 Q. All right. For surfactants, what is the role of
11 surfactants in the Astelin formulation?

12 A. Well, again as I explained for the Flonase
13 formulation, the surfactant in that is a wetting agent to
14 help the undissolved solid mix well into the water vehicle.

15 In the case of Astelin, the azelastine
16 hydrochloride and the other materials in that formulation
17 are already in solution, so they don't need something to
18 improve their ability to reside in the water phase, so there
19 is no surfactant that is included in Astelin.

20 Q. Okay. We have entered that in the chart. Let's go
21 to the next category, thickening agents. Does the Astelin
22 label provide information about thickening agents?

23 A. Yes, it does.

24 Q. What is the thickening agents that is used with
25 Astelin?

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1 A. It contains a thickening agent called
2 hydroxypropylmethylcellulose. And we abbreviated it as
3 HPMC, and that is a very commonly recognized abbreviation
4 for that material.

5 Q. So in Astelin, you said it is not a suspension, so
6 what is the thickening agent used in Astelin, if not to use
7 in suspension?

8 A. In this case, the thickening agent is used as part of
9 this nasal spray delivery system to enable the spray
10 droplets to be retained on the surface of the nasal mucosa
11 for a slightly longer period of time and not have the user
12 sense that it was dripping out of their nostrils to the back
13 of their throat.

14 Q. Is there other information in the art relevant to
15 azelastine hydrochloride about thickening agents that can be
16 used with that compound?

17 A. Yes, there is.

18 Q. And where did you find that?

19 A. Again, that is in the Astelin patent or the Hettche
20 patent.

21 Q. We brought that. Let's identify this as slide
22 DDX-5.17. And it has on it again DTX-16. This time at
23 column 4, lines 51 to 66.

24 And what have you called out in that section of
25 the patent?

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1 A. This is a section of the patent that describes the
2 desirability of adding thickening agents to a solution.
3 Again, for that, as they say, to prevent the solution from
4 flowing out of the nose too quickly and example agents are
5 provided in the paragraph to include cellulose derivatives
6 and gives a number of examples.

7 And one of things that I have highlighted is the
8 inclusion of both carboxymethylcellulose and
9 hydroxypropylmethylcellulose and
10 hydroxypropylmethylcellulose is the material, the HPMC that
11 is included in the Astelin and carboxymethylcellulose, I
12 will remind everyone that is the CMC part of the MCC/CMC
13 mixture that is included in Flonase.

14 Q. Okay. And the Astelin patent says that those, among
15 a number of other thickening agents, are appropriate for use
16 with azelastine hydrochloride?

17 A. That is what the patent directs, yes.

18 Q. All right. Let's go back to our chart. Have we
19 entered that information on the chart?

20 A. Yes.

21 Q. All right. Tonicity adjuster. Does the Astelin
22 patent, excuse me, the Astelin product use a tonicity
23 adjuster?

24 A. Yes, it does include a tonicity adjuster.

25 Q. What is the tonicity adjuster that is used?

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1 A. It uses sodium chloride as a tonicity adjuster.

2 Q. That is just salt?

3 A. Just salt, yes.

4 Q. Is that it a common tonicity adjuster?

5 A. It is also a very common tonicity adjuster.

6 Q. And does the art tell us anything about whether there
7 are other tonicity adjusters that can be used with
8 azelastine hydrochloride?

9 A. Yes, it does.

10 Q. And where did you look in the art for that
11 information?

12 A. The Hettche patent contains some other suggested
13 tonicity adjusting agents.

14 Q. And this is slide DDX-5.20. Again, for the record,
15 DTX-16 at column 4, lines 31 to 35.

16 And what have you called out there?

17 A. I called out the section talking about adjusting the
18 tonicity or the desire to adjust the tonicity of the
19 formulations containing azelastine hydrochloride. And,
20 here, the inventor lists saccharose, glucose, glycerine,
21 sorbitol, propylene glycol, and sodium chloride.

22 Q. When we say isotonization agents, is there any
23 difference between that and a tonicity adjuster?

24 A. No, there is not.

25 Q. All right. And so the Astelin patent teaches the use

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1 of these isotonization agents or tonicity adjusters with
2 azelastine hydrochloride; is that correct?

3 A. That is correct.

4 Q. We have to add that on the chart.

5 A. Yes.

6 Q. All right. Does the art -- well, strike the
7 question. Let's go to pH now.

8 What does the label tell us about the pH of the
9 Astelin formulation?

10 A. The pH of the formulation is given on the label, and
11 it tells us that the pH is 6.8 plus or minus 0.3 for that
12 product.

13 Q. Okay. So you now have all the information from the
14 label, the relevant information from the labels of Flonase
15 and Astelin. In making this combination product that you
16 have been asked to make, Dr. Donovan, what does the
17 formulator do next?

18 A. Well, examining the list, in this sort of comparator
19 format, it allows me to easily look at the materials and
20 their purposes and make some decisions about how I might
21 want to combine both the active ingredients and the other
22 excipient ingredients to develop a formulation that contains
23 both fluticasone propionate and azelastine hydrochloride.

24 Q. Okay. And have we put another column here on your
25 chart?

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1 A. Yes. And this one, this is what I call the obvious
2 combination formulation, because I'm using information from
3 the prior art and from the labels of the two commercially
4 available products at the time of 2002 to come up with what
5 as a strategy I would go forward with as a formulator.

6 Q. All right. And so let's start with the active
7 ingredient. What would the formulator take from the
8 information that has been provided in the labels and the
9 other prior art about what the active ingredient should be
10 and what their dosages should be?

11 A. I have essentially used the same active ingredients
12 at the same concentrations or dosage levels that were
13 present in each of the individual products already approved
14 in the marketplace.

15 Q. Okay. Is that something novel to the person of
16 ordinary skill in the art?

17 A. No.

18 Q. Okay. What is the particle size that the person of
19 skill in the art would select?

20 A. Well, understanding that, first, azelastine doesn't
21 have a particle size so I don't have to worry about that,
22 but I do have to be concerned about the particle size, and I
23 know that particle size does affects suspension quality and,
24 as a result, since there was a successful suspension product
25 already available, I would choose to use the same microfine

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1 fluticasone propionate in this obvious combination
2 formulation.

3 Q. Okay. And we have entered that on the chart.

4 Is there an obvious selection for the vehicle?

5 A. Water was the vehicle in both of the other agents,
6 and it is the preferred vehicle for nasal spray, so water
7 would be the obvious vehicle to use.

8 Q. And how about preservatives? Is there an obvious
9 selection for the person of skill in the art of
10 preservatives for use in a combination formulation?

11 A. Again, a POSA recognizes the importance of including
12 a preservative if they are going to be formulating for a
13 multidose system. And in this case, both of the products
14 Flonase and Astelin use benzalkonium chloride. And again,
15 that is a very popular and well understood antimicrobial
16 preservative, so I certainly would include that.

17 Both other agents act as adjuvants and act in
18 their, as individual materials, as antimicrobials, so you
19 need to preserve this particular combination product. They
20 are all possibilities for inclusion along, along with
21 potentially others, but the three that are already present
22 in those previous successful formulations would be three
23 preservatives to consider for addition, and I would, I would
24 put them in my list of materials for the obvious combination
25 formulation.

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1 Q. All right. So we put that up there. You have also
2 put after each a volume or concentration, I should say, and
3 how did you determine the concentration?

4 A. Those concentrations are given, they're based on the
5 concentrations that are either in Flonase or in Astelin or
6 the information about the concentration of EDTA that I
7 obtained from the Astelin patent or Hettche patent.

8 Q. Let me ask, if you hadn't had that information about
9 concentration, is the concentration of preservative
10 necessary within the level of skill of a person of ordinary
11 skill in the art to determine for a formulation?

12 A. There are a number of monograph sources that make
13 suggestions for what starting or what concentrations or
14 typical concentrations of antimicrobial preservatives are.

15 Formulators, typically when they are making a
16 final formulation, they do something called a preservative
17 challenge test to assure that the preservative combinations
18 and levels that they have selected are sufficient. So in
19 that case, the formulation itself is challenged with
20 bacteria; and then we look to see what bacteria grows or
21 whether there isn't growth and we go back and evaluate
22 increasing our preservatives if we didn't meet the standard
23 of the preservative challenge test.

24 That challenge, that preservative challenge test
25 usually gets done in later phase formulation development

1 then for each individual formulation, but there are ways
2 of choosing among preservatives or altering preservative
3 combinations to meet the means and the goals of that
4 preservative challenge test.

5 Q. So a person of ordinary skill, can they determine the
6 appropriate level of preservatives even if they are not
7 given a number like we have in this case?

8 A. Yes, they can.

9 Q. All right. So let me ask you this. With respect to
10 EDTA, that is not used in the Flonase formulation; correct?

11 A. Correct.

12 Q. Is there any reason to believe for the person of
13 ordinary skill in the art that EDTA would not work with
14 fluticasone propionate?

15 A. Knowing about the chemistry of those two molecules,
16 there is not an immediate reason for a person of skill in
17 the art to be concerned about combining them. And there
18 is also information that is known that other similar
19 corticosteroid materials have been combined with EDTA
20 successfully, so a person of ordinary skill in the art
21 would feel there would be a reasonable chance of success of
22 combining EDTA with fluticasone propionate.

23 Q. Okay. And by the same token, phenylethyl alcohol is
24 not used in Astelin. Is there any reason appearing in the
25 art at the relevant time to believe that phenylethyl alcohol

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1 will not work appropriately with azelastine hydrochloride?

2 A. No. Again, based on prior art and based on knowledge
3 of those structures, there is no reason for a POSA initially
4 to be concerned about that combination and they would be,
5 they would feel that they would be successful combining
6 azelastine hydrochloride with phenylethyl alcohol at those
7 concentrations.

8 Q. So given the prior art that you have referred to, do
9 you have a conclusion about whether the selections you have
10 made in the third column would have been obvious to a person
11 of ordinary skill in the art?

12 A. Again, yes. I think they are obvious there to use
13 them. There is no particular concern with exposing the
14 opposite drug molecule to one of the components, the
15 antimicrobial preservatives that were included in the other
16 drug products that we're using to guide our formulation
17 development.

18 Q. All right. Let's go to surfactants. Is there an
19 obviously selection for surfactants in this formulation?

20 A. Yes. There is no surfactant included in the Astelin
21 product and none needed, but there is one, there is a
22 surfactant needed or it would be very useful to the combined
23 product. The combined product is also going to be a
24 suspension and as a result including polysorbate 80 would be
25 the most obvious choice.

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1 Q. All right. So let me ask you this. Polysorbate 80
2 is not used with Astelin. Is there any reason appearing in
3 the art at the relevant time, 2002 or before, that indicates
4 that it would be a problem to use polysorbate 80 with
5 azelastine hydrochloride?

6 A. No, there is nothing in the art that suggests there
7 would be any problem with polysorbate 80 in the presence of
8 azelastine or azelastine hydrochloride. Polysorbate 80 gets
9 used with a lot of different materials, again, in
10 pharmaceuticals and in food products, and so a formulator
11 would feel quite, quite positive about including polysorbate
12 80 and not having any unanticipated problems with that
13 inclusion at the concentrations and typically used for
14 wetting agents.

15 Q. Okay. Let's go to thickening agents, and I won't
16 repeat the names of the thickening agents for the two
17 formulations that we've already gone through. But how would
18 the person of ordinary skill in the art think about
19 selecting a thickening agent?

20 A. Well, a formulator understands that those thickening
21 agents are even HPMC and MCC/CMC, these are cellulose based.
22 There are other ones suggested in the Astelin patent
23 certainly. And again they're there to provide the kind of
24 textural thickness that you desire for both suspendability
25 and for retention in the nasal cavity.

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1 For simplicity's sake, the obvious
2 combination formulation to start with is since we know that
3 MCC/CMC works very well as a thickening suspending agent in
4 Flonase, that would be a very logical obvious choice to
5 incorporate into the obvious combination formulation. The
6 Astelin patent also tells us that Astelin can be combined
7 with CMC.

8 So, again, it makes a lot of sense to start with
9 MCC/CMC, but we have knowledge that there are plenty of
10 other thickening agents if we so chose to use a different
11 material.

12 Q. Okay. And so you reference that the Astelin patent
13 makes reference to CMC. It doesn't make reference to
14 MCC/CMC; is that correct?

15 A. It doesn't make direct reference to that particular
16 Avicel material, but microcrystalline cellulose itself is an
17 insoluble material. It's present in very small particulate
18 size in this Flonase product. It's also used with a lot of
19 different drug agents both in solid dosage forms and is
20 quite compatible with many, many different molecules, and so
21 there really isn't a reason to believe that combining it
22 with azelastine hydrochloride would have any ill
23 consequences.

24 Q. And have you looked in the art for information about,
25 further information about MCC/CMC?

1 A. Yes.

2 Q. Where did you look for that?

3 A. I looked in a source called "The Handbook of
4 Pharmaceutical Excipients."

5 Q. Let me stop you right there. So I can identify it
6 for the record, this is slide DDX-5.28, which has an image
7 of DTX-62 at page 13.

8 Could you first describe what the reference is
9 that's pictured here?

10 A. "The Handbook of Pharmaceutical Excipients," and the
11 picture here is the second edition available prior to 2002,
12 and this is essentially a monograph source. It contains a
13 compilation of monographs of commonly used excipients. And
14 those monographs give us information about the chemical
15 structure and chemical characteristics and behaviors and
16 typical uses in formulations and oftentimes typical
17 concentrations or amounts that are used in particular
18 types of delivery systems or dosage forms and some
19 additional information potentially on other things of
20 importance.

21 Q. I see. So what is the excerpt that you've pulled out
22 here?

23 A. This is an excerpt that specifically describes
24 microcrystalline cellulose and carboxymethylcellulose in
25 combination. And, again, the family name Avicel and several

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1 different grades of Avicel that contain both MCC/CMC are
2 commercially available, gives us some information about the
3 substance. And it tells us or tells the formulator that
4 the microcrystalline carboxymethylcellulose, or
5 microcrystalline cellulose and carboxymethylcellulose
6 product known as Avicel is dispersible in water. It
7 produces a thixotropic gel and are used frequently as
8 suspending vehicles, which is exactly how they are used
9 in Flonase and would be use in the obvious combination
10 products.

11 Q. All right. And is it within the level of skill in
12 the art for a formulator to determine the amounts of
13 thickening agents to use in your combination product?

14 A. Yes. Certainly, it is, and there are, again,
15 monograph sources that tell you what typical concentrations
16 to use for the agent for a particular type of viscosity that
17 you might desire.

18 Q. Okay. And let's go back to the chart. And what have
19 you filled in here for thickening agents in your combination
20 formulation?

21 A. In, again, as I said, any of the thickening agents
22 that were mentioned in Astelin patent or are present in
23 those two products would likely be a suitable thickening
24 agent. And so I've got MCC/CMC, Avicel placed in the
25 obvious combination formulation. HPMC would also be an

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1 obvious thickening agent.

2 Q. Okay. Let's go to the tonicity adjusters, and I
3 won't read all of them into the record, but how would a
4 person of ordinary skill in the art analyze tonicity
5 adjusters for the combination formulation?

6 A. Looking at the tonicity adjuster in Flonase, looking
7 at the tonicity adjuster in Astelin, knowing about other
8 tonicity adjusters, and even knowing that the Astelin patent
9 directed the use of a number of tonicity adjusters,
10 typically, a formulator looks at the possibilities for
11 tonicity adjusters and makes a choice again in mid to late
12 stage formulation development, which among those would be
13 appropriate for tests which among those would be an
14 appropriate tonicity adjuster.

15 Again, all we're doing is adding dissolved
16 solute into the vehicle to adjust the tonicity. So choosing
17 among the tonicity adjusters is usually quite simple and is
18 just done by routine experimentation.

19 Q. Okay. And so you have on your chart, you have a
20 group of tonicity adjusters. What's your opinion on the
21 selection of any one of those adjusters?

22 A. I would likely leave it open to choose among any of
23 them depending on, as I was starting to build my obviousness
24 combination formulation, what I would at the time decide
25 that I was going to include to adjust the tonicity. So any

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1 of those listed would be certainly good choices. There's no
2 reason to choose one over another necessarily, and as a
3 formulator I would probably wait and see how my formulation
4 was coming together to choose.

5 Q. Is there information in the art that you brought with
6 you today that talks about the amount of a tonicity adjuster
7 that might be appropriate for this formulation?

8 A. Yes, there is.

9 Q. Okay. And this is, for the record, DDX-5.30. It's a
10 side number, and the exhibit is DTX-62 at page 22.

11 And, again, would you identify first the
12 reference that we're talking about here?

13 A. This is a monograph from the "Handbook of
14 Pharmaceutical Excipients," and this happens to be the
15 monograph about glycerin, one of the tonicity adjusters that
16 was described in the Astelin patent.

17 Q. Okay. And what information does it provide about the
18 amount of glycerin?

19 A. It tells a formulator that a 2.6 percent
20 volume-volume concentration in water, that that mixtures
21 will be iso-osmotic with serum. For simplicity's sake, it's
22 essentially the same thing as isotonic in this case. And
23 it tells a formulator that they certainly wouldn't need to
24 add more than 2.6 percent of glycerin into a formulation to
25 make it isotonic if that was their desire, and they would

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1 likely add less, because there would likely be other
2 materials in solution already. So they would add an amount
3 less than 2.6 percent if their goal was to achieve an
4 isotonic formulation.

5 Q. Okay. And have you completed the chart for tonicity
6 adjusters as well?

7 A. Yes, I have.

8 Q. And have you put in an amount adjacent to glycerin
9 there?

10 A. I did, just because the monograph helps us know a
11 good starting point for a concentration of glycerin.

12 Q. Okay. Is it your conclusion that any of those
13 selections that we've included would have been obvious to a
14 person of ordinary skill in the art?

15 A. Yes.

16 Q. Assume that the amount of glycerin was not provided.
17 Is it within the level of skill in the art for a formulator
18 to determine the amount of a tonicity adjuster that is
19 required in a formulation?

20 A. Yes, and that's usually done experimentally as a -- a
21 formulation is becoming more and more finalized, as we're
22 sure which materials are in solution, at what
23 concentrations. Then we'll choose a tonicity adjuster
24 to then balance the tonicity to whatever target goal we
25 had.

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1 Q. All right. Let's go to pH. How would a person of
2 skill in the art determine the appropriate pH level for this
3 combination formulation?

4 A. Well, I look at the pH ranges for Flonase, 5 to 7,
5 and Astelin, a narrower pH range of 6.8. And certainly 6.8
6 is within the range of Flonase, so that already tells me
7 that I could likely stick with that as a value.

8 As a formulator, I also know though that
9 I'd like to have as broad a pH range as possible to work
10 with. It allows me a lot of flexibility as I optimize my
11 formulation to add materials or substitute materials in the
12 system.

13 So I have knowledge of what the, what a --
14 a typical appropriate pH range for nasal formulations would
15 be, and as a formulator I would have at the point of initial
16 formulation development leave open the possibility for a
17 relatively broad range of pHs and then bring back in that I
18 know what the pH ranges for the two products are, and if
19 those were important to go back to, I could certainly narrow
20 my range as I was working with the formulation.

21 Q. Does the art provide some information about what an
22 appropriate pH range is for nasal formulations?

23 A. Yes, it does.

24 Q. All right. And for the record, this is slide
25 DDX-5.32 and we have Exhibit DTX-78 at page 19. Can you

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1 identify the reference for the record first and then we'll
2 talk about the callout.

3 A. Sure. This is another cite to the "Art, Science and
4 Technology of Pharmaceutical Compounding" by Lloyd Allen,
5 and, again, an excerpt from the chapter on nasal products.

6 Q. All right. And what does this excerpt at page 19,
7 which is -- which has a heading pH and buffering, tell you
8 about the appropriate pH range to work with?

9 A. As underlined at the bottom of that section, there's
10 a summation of the discussion that it's generally reasonable
11 for a pH range of four to eight to be considered optimum for
12 a nasal formulation, which tells a formulator that again I
13 have a fairly broad range of pHs that I can anticipate using
14 successfully with my nasal formulation.

15 Q. Now, assuming that you didn't have information like
16 this, is it within the range, the range of ordinary skill in
17 the art for a formulator to determine an appropriate pH for
18 formulation?

19 A. Well, with the knowledge of what an acceptable pH
20 range or if one needed to do experimentation, one could do
21 that to determine whether their pH was acceptable. Yes,
22 that's something that a formulator participates in on a
23 frequent basis.

24 Q. Okay. Let's go back to your obvious combination
25 formulation. And what have you filled in there as the

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1 obvious pH range for this combination formulation?

2 A. I put in the broadest range possible as a starting
3 point with, again, a note that if that needed to be
4 adjusted, it's well-known in the art how to adjust the pH of
5 a formulation, and if the pH needed to be kept in a very
6 narrow range in that formulation, the addition of buffer
7 systems into that formulation would also be known and
8 appropriate.

9 Q. All right. Now, we've completed your obvious
10 combination formulation or at least that column there. Let
11 me ask you a few summary questions about this. Are all the
12 ingredients, whether active or excipients in that column,
13 present in the prior art?

14 A. Yes, they are.

15 Q. Would a POSA, person of ordinary skill in the
16 art, be able to determine the amount of each of the
17 ingredients to use?

18 A. They -- they would.

19 Q. Would a person of ordinary skill in the have been
20 motivated to combine them?

21 A. Yes, they would.

22 Q. And would a person of ordinary skill in the art have
23 had any expectation about whether this formulation could be
24 made?

25 A. I think based on the success of the individual

Donovan - direct

1 formulations and the knowledge of the chemical systems and
2 the knowledge of materials, yes, that a person of ordinary
3 skill in the art would have certainly a reasonable
4 expectation to be successful with that obvious combination
5 formulation.

6 Q. All right. And you said obvious. I'm going to ask
7 you directly: Have you reached a conclusion about whether
8 that combination formulation would be obvious to the person
9 of ordinary skill in the art as of 2002 given the prior art
10 that you have been reviewing?

11 A. Yes. I believe based on just the simple way that
12 we've gone through the label information and prior art, that
13 that is an obvious formulation, obvious combination
14 formulation for those materials.

15 Q. Okay. Doctor, I'm going to change gears here and
16 we're going to go to the claims in the case and consider the
17 claims. That's part of your analysis here; is that right?

18 A. That's correct.

19 Q. And how many claims has plaintiff asserted in this
20 case?

21 A. I'm sorry. I can't remember, but it's a lot.

22 Q. All right. 15. Does that sound right?

23 A. That sounds right to me, yes.

24 Q. All right.

25 A. Thanks.

Donovan - direct

1 Q. So let's talk about how we're going to go through
2 these 15 claims. I'm just going to identify this chart
3 first and have you walk us through how you used it. It's
4 DDX-5.34 at the first slide. At the top, it indicates that
5 it's dealing with the 428 patent, claim 11.

6 And just generally before we talk specifically
7 about claim 11, would you describe the information on the
8 page and how you're going to be using it, because we're
9 going to see a few slides like this.

10 A. Sure. Okay. What should be familiar is the
11 left-hand side of that slide contains the summation of the
12 obvious combination formulation along with its likely, the
13 role of those excipients or actives in the obvious
14 combination formulation. So we've taken that from the
15 previous table and moved it over here to make it easy for us
16 to compare among the information provided in the claim. And
17 then in the center section are the relevant claims that I
18 want to discuss on each side.

19 In the case of this slide, we chose claim
20 11 from the '428 patent because claim 11 was quite specific
21 in the contents and concentrations of the materials included
22 in the formulation, so it was a good place to start.

23 In the case of claim 11, since it's dependent on
24 claim 1, claim 1 is also included on the slide. And then
25 after, going through an analysis of reading the claims,

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1 reading what the claims describe and then comparing it to
2 the obvious combination formulation, the final determination
3 in the right-hand side, would that claim have been obvious
4 from that obvious, that obvious formulation?

5 The other thing to point out is the materials
6 that are listed in red in the table of the obvious
7 combination formulation are really the materials that are
8 the subject of that particular claim, so those will change
9 as I go through different claims, because each of the claims
10 discusses a different combination of materials in the
11 formulation.

12 Q. Okay. Thank you, Doctor.

13 Before we launch into this, just with respect to
14 claim 11, which depends from claim 1, you can see generally
15 they have the two active ingredients and then the excipients
16 that we've been talking about detailed there.

17 Do you have an understanding that the Dymista
18 product is an embodiment of the claims of the
19 patent-in-suit?

20 A. Yes, that's what I understand.

21 Q. And just, let me just ask you: In the Dymista
22 product, are the excipients used consistently with the way
23 they're taught to be used in the prior art?

24 A. Yes, they are.

25 Q. All right. So let's start in on this, Doctor.

Donovan - direct

1 So claim 11, we're talking about specifically.

2 Let me ask you this: Have you reviewed all of the elements
3 of claim 11?

4 A. Yes, I have.

5 Q. And have you determined whether they're in the
6 formulation that you consider obvious based on the art?

7 A. Yes, they are.

8 Q. And have you indicated that on this slide?

9 A. Yes, I have.

10 Q. And in your opinion, would a person of ordinary skill
11 have been motivated to combine these elements in the claimed
12 way?

13 A. Yes, they would.

14 Q. And in your opinion, would a person of ordinary skill
15 in the art have had a reasonable expectation the combination
16 would work?

17 A. Yes, they would.

18 Q. What's your opinion about whether the method of claim
19 11 of the '428 patent would have been obvious at the time of
20 the priority date?

21 A. The method of claim 11 would have been obvious.

22 Q. Let's go to the next slide, DDX-5.35. And this time
23 it's referring to claim 10; is that right?

24 A. Yes. I'm sorry, yes.

25 Q. And it has two other claims there because claim 10

Donovan - direct

1 depends from them; is that right?

2 A. Right.

3 Q. And in red on the left-hand side in your obviousness
4 formulation are the elements that are in these particular
5 claims; is that right?

6 A. That's right.

7 Q. All right. And what did you do with respect to
8 claim 10?

9 A. Okay. I looked at claim 10, looked at the
10 ingredients that were described in claim 10 and their
11 concentrations described in the claim, compared it to the
12 obvious combination formulation. And the concentrations
13 identified for the obvious combination formulation and
14 following that comparison found that all of the ingredients
15 described in claim 10 are included in the obviousness
16 combination formulation, and as a result, believe that that
17 -- and find that that claim is obvious.

18 Q. Okay. And just for the record, would a person of
19 ordinary skill in the art have been motivated to combine the
20 elements of claim 10 as they have been combined in the
21 claim?

22 A. Yes, they would have been.

23 Q. And would there be an expectation of success?

24 A. Yes, there would be.

25 Q. All right. Let's go to the next slide, DDX-5.36. On

Donovan - direct

1 this slide you have -- it's for claim 13, first of all; is
2 that right?

3 A. That's correct.

4 Q. You've underlined some information in green and
5 highlighted some information in green in the left-hand
6 column about your obvious formulation. What is the green
7 signifying?

8 A. This is again trying to be helpful to point out the,
9 the -- the important change in this claim as compared to
10 other claims. And in this claim, the description of the
11 amounts of azelastine hydrochloride and fluticasone
12 propionate are included in terms of mass of the active
13 ingredients rather than concentration, and previously, as we
14 were developing the table that got us to be able to describe
15 the obvious combination formulation, we had already
16 converted the concentration information from the product
17 into appropriate mass units or concentration units to make
18 again this portion simpler.

19 So in this case claim 13 is describing a mass
20 range for the dose of azelastine hydrochloride and a mass
21 range for the dose range of fluticasone propionate, and
22 those masses are found in the obvious combination
23 formulation, which then brings me to conclusion that that
24 claim 13 is obvious.

25 Q. Okay. So do you agree with all of the elements of

1 claim 13?

2 A. Yes, I have.

3 Q. And are they all found in the prior art?

4 A. Yes, they are.

5 Q. And would a person of ordinary skill have been
6 motivated to combine them?

7 A. Yes, they would.

8 Q. Would there have been a reasonable expectation of
9 success?

10 A. Yes, there would.

11 Q. Let's go to the next one, claim 15. And for the
12 record, this is DDX-5.37. And I should note because I
13 didn't before, on each of these slides there's a reference
14 at the top of the left-hand column of the references that
15 are the basis for your statements about the prior art; is
16 that right?

17 A. That's correct.

18 Q. All right. I will just read them into the record:
19 Flonase has the Astelin patent, the handbook that we looked
20 at and the Allen reference.

21 A. Right.

22 Q. Do you need another drink?

23 A. No.

24 Q. Claim 15. Have you reviewed all of the elements of
25 claim 15?

1 A. Yes, I have.

2 Q. And are all of those elements present in the prior
3 art?

4 A. Yes, they are.

5 Q. And would there have been a motivation for a person
6 of ordinary skill in the art to combine them?

7 A. Yes, there would be.

8 Q. And would there be an expectation of success, a
9 reasonable expectation of success?

10 A. Yes, there would be.

11 Q. And just for the record, the only thing that's new
12 about this is the pH range; is that correct?

13 A. That's correct.

14 Q. Let's go to claim 16, DDX-5.38. Claim 16, what's the
15 only thing new that we have not really talked about before
16 in this one?

17 A. In this case, claim 16 describes an aqueous
18 suspension.

19 Q. All right. Have you reviewed all the elements of
20 claim 16?

21 A. Yes, I have.

22 Q. Have you determined whether they're in the
23 formulation that you have considered to be obvious based on
24 the prior art?

25 A. Yes, I have.

Donovan - direct

1 Q. Would a person of ordinary skill in the art have been
2 motivated to combine them?

3 A. Yes, they would be.

4 Q. And would that person of ordinary skill in the art
5 have had a reasonable expectation that they would work?

6 A. Yes, they would.

7 Q. What's your conclusion about whether the method the
8 claim would have been obvious at the time of the priority
9 date?

10 A. I conclude that claim 16 is obvious.

11 Q. All right. Let's go to the next one. Claim 23.
12 This is DDX-5.39. Have you reviewed the elements of claim
13 23?

14 A. I have.

15 Q. Did you determine whether they're all in the art or
16 not?

17 A. They are.

18 Q. Are they in your obvious formulation?

19 A. They are contained in my obvious formulation.

20 Q. Would a person of ordinary skill in the art have been
21 motivated to combine these elements in the claimed way?

22 A. Yes, they would be.

23 Q. Would that person have had a reasonable expectation
24 of success that the combination would work?

25 A. Yes, they would.

Donovan - direct

1 Q. What is your opinion on the obviousness of claim 23?

2 A. My opinion is claim 23 is obvious.

3 Q. Let's go to the next slide. DDX-5.40, claim 24.

4 Have you reviewed the elements of claim 24?

5 A. I have.

6 Q. And have you determined whether or not those elements
7 are all in the prior art?

8 A. Yes, I have.

9 Q. Are they in your obvious formulation?

10 A. They are.

11 Q. Would a person of ordinary skill in the art have been
12 motivated to combine these elements in the claimed way?

13 A. They would be.

14 Q. In your opinion, would a person of ordinary skill in
15 the art have a reasonable expectation the combination would
16 work?

17 A. Yes, they would have a reasonable expectation it
18 would work.

19 Q. What is your opinion about the obviousness of claim
20 24?

21 A. My opinion is claim 24 is obvious.

22 Q. Let's go to claim 26. This is DDX-5.41.

23 Have you reviewed the elements of claim 26?

24 A. Yes, I have.

25 Q. Is there anything really new about claim 26 as

Donovan - direct

1 opposed to the other claims we have been talking about?

2 A. To a layperson, it doesn't seem to be to me.

3 Q. All right. So claim 26, have you reviewed all the
4 elements of claim 26 and compared them to the prior art?

5 A. Yes, I have.

6 Q. Are they present in the prior art?

7 A. Yes, they are.

8 Q. Are they present in the formulation you consider
9 obvious based on the prior art?

10 A. Yes, they are.

11 Q. Would a person of ordinary skill in the art have been
12 motivated to combine these elements in the claimed way?

13 A. Yes, they would.

14 Q. Would a person of ordinary skill in the art have had
15 a reasonable expectation that they would work?

16 A. Yes, they would.

17 Q. What is your opinion about whether the method of
18 claim would have been obvious at the time of the priority
19 date?

20 A. My opinion is claim 26 would be obvious.

21 Q. Let's go to claim 29.

22 Again, is there anything new about this claim
23 really as opposed to the other ones that we have been
24 talking about?

25 A. Nothing significant, no.

Donovan - direct

1 Q. Have you considered whether all the elements of claim
2 29 are present in the prior art?

3 A. Yes, I have.

4 Q. What is your conclusion?

5 A. My conclusion is based on the obvious combination
6 formulation that a POSA would be motivated to make and would
7 have a reasonable expectation of success that the
8 description of claim 29 is obvious.

9 Q. And what is your conclusion about whether claim 29 is
10 obvious?

11 A. That is obvious, yes.

12 Q. All right. Let's go to claim 30.

13 And have you compared all the elements of claim
14 30 to the prior art?

15 A. Yes, I have.

16 Q. And have you compared them to your prior art, the
17 formulation you consider obvious based on the prior art?

18 A. Yes, I have.

19 Q. And have you come to a conclusion about a person,
20 whether a person of ordinary skill in the art would be
21 motivated to combine those elements in the claimed way?

22 A. Yes, I believe a person of ordinary skill in the art
23 would be motivated to combine them in that way.

24 Q. Have you come to a conclusion about whether a person
25 of ordinary skill in the art would have a reasonable

Donovan - direct

1 expectation about whether that combination would work?

2 A. Yes, they would have a reasonable expectation of
3 success of that obvious formulation.

4 Q. Did you come to a conclusion about the obviousness of
5 claim 30?

6 A. Claim 30 is obvious.

7 Q. Okay. Doctor, we have completed one of the patents.
8 Let's go to the next patent. This is the '620 patent. And
9 just in a general sense, what is the difference between the
10 '620 patent and the patent we just looked at?

11 A. The previous patent contains more detail about
12 concentration ranges in specific and included materials.

13 Q. Okay. And these are pharmaceutical formulation
14 terms -- claims; is that right?

15 A. Yes, they are.

16 Q. So have you looked at the elements of claim 42 of the
17 '620 patent?

18 A. Yes, I have.

19 Q. And just so that we have an idea what we're looking
20 at here, claim 1, from which it depends, states the active
21 ingredients; is that right?

22 A. Yes, it does.

23 Q. And claim 42, what in general does that have?

24 A. It describes the formulation and the agents included
25 in the formulation that would then contain those two active

1 ingredients.

2 Q. Have you looked to determine whether all the elements
3 of claim 42 are in the prior art?

4 A. Yes, I have.

5 Q. Have you determined whether they are actually in
6 the formulation that you consider obvious based on the
7 references we talked about?

8 A. They are in the obvious combination formulation that
9 I identified.

10 Q. Would a person of ordinary skill in the art have been
11 motivated to combine these elements in the combined way?

12 A. Yes, they would.

13 Q. In your opinion, would a person of ordinary skill in
14 the art have a reasonable expectation they would work?

15 A. Yes, they would.

16 Q. What is your opinion about the obviousness of the
17 claimed formulation?

18 A. I believe that claim 42 and its claim 41 are obvious.

19 Q. Let's go to claim 43.

20 And I guess we have underlined "nasal spray"
21 here.

22 A. Yes.

23 Q. All right. Have you gone through the elements of
24 claim 43 to determine whether all those elements are present
25 in the prior art?

Donovan - direct

1 A. They are.

2 Q. Are they present in the formulation you consider
3 obvious based on the prior art?

4 A. Yes, they are.

5 Q. Can you tell me whether all the elements from claim
6 43 are present?

7 I just asked you that. I'm sorry.

8 Would a person of ordinary skill in the art have
9 been motivated to combine those elements?

10 A. Yes, they would be.

11 Q. Would they have a reasonable expectation of success?

12 A. Yes, they would.

13 Q. What is your opinion about whether the combination
14 would have been obvious at the time of the priority date?

15 A. I believe that claim 43 would be obvious.

16 Q. Let's go to claim 44.

17 Have you looked at all the elements of claim 44?

18 A. Yes, I have.

19 Q. Are all those elements in the formulation you
20 consider obvious based on the prior art?

21 A. Yes, they are.

22 Q. Would a person of ordinary skill in the art been
23 motivated to combine them all?

24 A. Yes, they would be.

25 Q. Would they have a reasonable expectation of success?

Donovan - direct

1 A. Yes, they would.

2 Q. Let's go to claim 4.

3 We have particle size now, Doctor. Does that
4 change your analysis at all?

5 A. No, it does not.

6 Q. Are all the elements of claim 4 present in the
7 formulation you consider obvious based on the prior art?

8 A. Yes, they are.

9 Q. All those elements, would a person of ordinary skill
10 in the art be motivated to combine those elements?

11 A. Yes, they would be.

12 Q. Would they have an expectation of success?

13 A. Yes, they would.

14 Q. A reasonable success?

15 A. A reasonable expectation of success.

16 Q. What is your conclusion about the obviousness of
17 claim 4?

18 A. That claim 4 would be obvious.

19 Q. Last claim, Doctor. This is claim 29, which depends
20 on claim 26, which depends on claim 6, which depends on
21 claim 5, which depends on claim 1.

22 Have you reviewed all the elements of claim 29?

23 A. Yes, I have.

24 Q. Are all those elements present in the formulation you
25 consider obvious based on your review of the prior art?

1 A. Yes, they are.

2 Q. Would a person of ordinary skill in the art have been
3 motivated to combine those elements in the claimed way?

4 A. Yes, they would be.

5 Q. Would that person have had a reasonable expectation
6 that the formulation could be made and would work?

7 A. Yes, they would.

8 Q. What is your opinion about whether the combination
9 would have been obvious at the time of the priority date?

10 A. That combination would have been obvious. And claim
11 29 is obvious as a result.

12 Q. And, Doctor, I believe we have completed all the
13 claims that plaintiffs have asserted in this case. Is that
14 your understanding?

15 A. That is my understanding.

16 Q. Okay. Let's change gears.

17 Your Honor, may I just grab a sip?

18 THE COURT: Certainly.

19 MR. LOMBARDI: I have a lozenge.

20 THE WITNESS: I'm fine. Thank you.

21 BY MR. LOMBARDI:

22 Q. I want to talk a little bit about some of the
23 positions that plaintiffs' experts have taken --

24 A. Okay.

25 Q. -- on the formulation points, Doctor.

Donovan - direct

1 Let's talk first, do you have an understanding
2 that plaintiffs' experts have expressed opinions about
3 whether a person of ordinary skill in the art would think
4 that you could combine an active ingredient that goes into
5 solution with an active ingredient that is a suspension in
6 the same formulation?

7 A. Yes, I'm aware that they have raised that as an
8 issue.

9 Q. And are you aware that they have taken the position
10 that that would be considered something problematic by a
11 person of ordinary skill in the art?

12 A. Yes, that is my understanding.

13 Q. Do you agree with that?

14 A. No, I don't.

15 Q. Is it unusual to have formulations that are
16 suspensions that also have ingredients that go into
17 solutions?

18 A. It is very common to have materials in solution when
19 one has a suspension. In fact, in all cases, there is even
20 whatever single material is undissolved has some number of
21 molecules dissolved in the vehicle.

22 Q. All right. And do you have any real world examples
23 you can give the Court of a situation where there is a
24 suspension that also include ingredients that go into
25 solution?

Donovan - direct

1 A. Yes, I do.

2 Q. What is that?

3 A. One of the simplest is the Flonase example we have
4 been talking about.

5 Q. All right. And did we -- we've got the Flonase label
6 back again. Let me identify for the record, it's DDX-5.49.
7 And on that is DTX-33 at page 2, lines 17 to 26.

8 That is the Flonase label we referred to before;
9 is that correct?

10 A. Yes, it is. And the excerpt is the region around the
11 inactive ingredients or the contents of the formulation.

12 Q. Okay. And so what does this label say relevant to
13 your point about suspensions in solution?

14 A. The label tells us again that it is an aqueous
15 suspension and that microfine fluticasone propionate is
16 suspended in the vehicle.

17 When I look at the rest of the ingredients it
18 tells me, for example, 0.02 weight volume benzalkonium
19 chloride is included in that formulation, and I know that is
20 below the solubility, that concentration is far below the
21 solubility of benzalkonium chloride in water, so that
22 material I know is in solution.

23 Similarly, for .025 percent phenylethyl alcohol,
24 a formulator, POSA formulator knows that that is below the
25 solubility limit of phenylethyl alcohol and, as a result,

Donovan - direct

1 that material is also in solution in that formulation.

2 Q. Is there anything else that you know in this Flonase
3 formulation that also goes into solution to some extent?

4 A. Well, I know there is some fluticasone propionate in
5 solution in equilibrium with the solid material that is in
6 the suspension; and I suspect many of the other materials
7 that are listed in the ingredient list are also in solution.

8 Q. Okay. Are there actually, are there any sources out
9 there that instruct POSA or that demonstrates that you can
10 make a suspension that includes ingredients that go into
11 solution?

12 A. There is plenty of those sources, yes.

13 Q. Have you brought an example here?

14 A. I have.

15 Q. Let's go to the next slide. DDX-5.50. It says
16 DTX-78, at pages 17 to 18.

17 We have seen this before, but can you identify
18 the reference for the record, please?

19 A. The reference is the Art, Science, and Technology of
20 Pharmaceutical Compounding by Loyd Allen.

21 Q. And you have pulled out a section that says there is
22 a box that is titled Preparation of Nasal Products. Do you
23 see that?

24 A. Yes.

25 Q. And what are you indicating about this box?

Donovan - direct

1 A. Okay. Well, this whole section is again excerpted
2 from the nasal product section of the text. And what the
3 preparation of nasal products sub-box is, is a description
4 from the author about how to prepare a suspension for nasal
5 administration.

6 Q. Okay. And I guess it's the first underlining within
7 the box. It says suspension; is that right?

8 A. Correct.

9 Q. All right. And then below that it gives various
10 steps?

11 A. Yes.

12 Q. And the second step you have highlighted. And why
13 did you highlight that?

14 A. Because that step is directing the formulator to
15 dissolve/mix, and the formulator would understand that to
16 mean that they should dissolve the ingredients that are
17 soluble and mix the ingredients that are not soluble, so
18 that there would be solid materials, thus the suspension.
19 And they should either dissolve or mix those contents in a
20 sub-quantity, and I think the author here says three-fourths
21 of the total volume of vehicle that they intend to use. So
22 that is an initial preparation step.

23 But it clearly specifies for materials that
24 would go in solution, they're going to dissolve materials
25 that are above their solubility limits. They get mixed as

1 suspension materials.

2 Q. Does a formulator make a distinction between whether
3 it is an active ingredient or an excipient for purposes of
4 whether you can have materials in solution and materials in
5 suspension in the same formulation?

6 A. No. Oftentimes, formulators treat all of the
7 materials in the formulation as chemical entities with
8 material properties that they are trying to combine in a
9 particular way for a particular goal. So whether it's
10 active or whether it's what we call an inactive ingredient,
11 we evaluate their chemical and material properties to move
12 us forward to make the preparation we desire to make.

13 Q. Are you aware of any authoritative sources that say
14 that there are any problems unique to formulations that mix
15 suspensions and solutions in the art as of the relevant
16 date, 2002?

17 A. No, I am not.

18 Q. Have you reviewed the report and testimony of
19 Dr. Smyth, plaintiffs' formulation expert?

20 A. Yes, I have.

21 Q. Have you reviewed the materials that he cites?

22 A. Yes, I have.

23 Q. Does he cite to any authoritative source that reports
24 that there is an issue with the formulation of, formulation
25 that includes ingredients in suspension, active ingredients

Donovan - direct

1 in suspension, active ingredients in solution?

2 A. No, he does not.

3 Q. Have you reviewed the patents in suit, the patents
4 that are asserted against Apotex in this case?

5 A. Yes, I have.

6 Q. Do those patents say anything about how to make a
7 formulation that includes active ingredients in suspension
8 and active ingredients in solution?

9 A. No. If they say anything, they direct to use
10 techniques known in the art.

11 Q. So no specific instructions?

12 A. No.

13 Q. Now, are there, in the art, examples of suspension
14 that, suspensions that include one active ingredient that is
15 formulated as a suspension with another active ingredient
16 that goes into solution?

17 A. Yes, there are.

18 Q. Can you give us one example?

19 A. Yes. I brought an example that includes azelastine
20 even as one of the materials in solution.

21 Q. Okay. And let's go to the next slide. DDX-5.51.

22 And this is DTX-12, at 7, page 7, lines 27 to 52.

23 And for the record, this is a European patent
24 application with the last three numbers 127. And it's a
25 reference we have seen before, Cramer. Is that correct?

Donovan - direct

1 A. Correct. It's the Cramer patent we talked about
2 earlier.

3 Q. And what have you pulled out from Cramer here?

4 A. This is an example that Cramer gives in his patent,
5 and it's an example where it's intended as a nasal
6 composition, intended for nasal administration, and it
7 contains triamcinolone acetonide, azelastine, polysorbate
8 80, glycerin, hydroxypropyl methyl cellulose.

9 Q. You don't have to read it.

10 A. All the rest of the materials we talked about in the
11 obvious formulation.

12 Q. All right. So which are the active ingredients in
13 the Example 3 table that you were just reading from?

14 A. The active ingredients would be considered
15 triamcinolone acetonide which is a corticosteroid material
16 very similar in function to fluticasone propionate and
17 azelastine hydrochloride, one of the materials we have been
18 discussing.

19 Q. And of those two active ingredients, does one go into
20 suspension?

21 A. Yes. Based on the weight concentrations provided in
22 the table, triamcinolone acetonide has very similar
23 solubility properties in general as does fluticasone
24 propionate, and at the same weight percent concentration as
25 we have seen in Flonase, that material is also going to be

1 in suspension.

2 Azelastine hydrochloride in comparison is in a
3 slightly lower concentration than what we have been talking
4 about and, thus, I know is in solution.

5 Q. So there is one active in suspension and one active
6 in solution; is that right?

7 A. That is correct.

8 Q. Is there any suggestion on the face of this reference
9 that there is a formulation problem particular to the fact
10 that there is a suspension that includes an active
11 ingredient in solution?

12 A. The inventor makes no mention of it, any difficulties
13 regarding Example 3.

14 Q. Okay. So what does this example tell the person of
15 ordinary skill in the art about formulating a suspension and
16 a solution in the same formulation?

17 A. It directs the reader to use known mixing techniques
18 to prepare that composition.

19 Q. Does this example make reference to other steroids
20 that could be used?

21 A. Yes, it does. In the paragraph that is below the
22 table describing the composition, it identifies other
23 suitable steroid materials to use, and fluticasone is one of
24 the materials that identifies, along with mometasone
25 budesonide and a few others.

Donovan - direct

1 Q. I didn't bring my pointer, but it is there about
2 the third line down from the table; is that correct?
3 Fluticasone.

4 A. Yes, it is.

5 Q. Does it talk about the ability to use other suitable
6 ingredients that the person of ordinary skill in the art
7 could choose?

8 A. Yes, it again directs the reader that this is an
9 example, and that persons of skill in the art or the reader
10 would be able to make suitable alterations and it would
11 still be within the scope of the invention.

12 Q. Okay. Now, as part of your work in this case, did we
13 ask you to take a look at a submission to the Patent Office
14 by the inventor of the patents in suit?

15 A. Yes, you did.

16 Q. And was that a submission that related to Cramer,
17 Example 3?

18 A. Yes, it was.

19 Q. And just in a general sense, and we're going to talk
20 in more detail about this, what was the inventor presenting
21 to the Patent Office?

22 A. The inventor presented some information and their
23 subjective opinion that they attempted or oversaw the
24 attempt to make Cramer Example 3 and found it to be
25 inoperable.

Donovan - direct

1 Q. Do you agree based, on the information that the
2 inventor provides, that Cramer Example 3 is inoperable?

3 A. No, I don't.

4 Q. All right. Let's talk about that in some detail.

5 Just the first question so we have the framework
6 here. What was the formulation that the inventor was
7 actually testing for purposes of the testing submitted to
8 the Patent Office?

9 A. The formulation was the formulation described in
10 Cramer Example 3 containing triamcinolone acetonide and
11 azelastine hydrochloride along with the other ingredients
12 specified in Example 3.

13 Q. Did that testing that the inventor did involve
14 fluticasone propionate?

15 A. No, it did not.

16 Q. Did it involve all of the excipients that are claimed
17 in the patents-in-suit that are to be used with fluticasone
18 propionate and azelastine hydrochloride?

19 A. No. It only involved the excipients that are
20 included in the table.

21 Q. All right. And you reviewed the testing that was
22 done by the inventor; is that right?

23 A. I reviewed the inventor's description of their --
24 their conclusions regarding the testing.

25 Q. And you're making a distinction there, so let me ask

Donovan - direct

1 you: Does it appear the inventor actually did the testing
2 herself?

3 A. I believe the inventor discloses that she oversaw
4 that testing.

5 Q. All right. And how many tests did the inventor
6 actually do?

7 A. It appears that only one test was performed.

8 Q. Is that relevant to your opinion as a formulator?

9 A. Yes.

10 Q. Why is that?

11 A. Well, especially as a formulator, knowing that even
12 the example directly reads that you could make changes as
13 needed to that formulation as seen fit, that only doing
14 that, only making that material once isn't really a test of
15 whether that Example 3 is operable or inoperable.

16 Q. All right. So when a formulator works on a
17 formulation, is it unusual, common, usual, whatever it is,
18 for a formulator to come up with a final operable
19 formulation in one try?

20 A. It's very unusual.

21 Q. And why is that?

22 A. Well, again, we are combining materials that we want
23 to combine and have the end result be something that we had
24 identified as a goal, and oftentimes we make initial -- we
25 declare initial concentrations or select particular

Donovan - direct

1 materials because we think they will work well and at times
2 when we actually observe the product that develops, that we
3 fully feel that there might be a way to improve that by
4 changing the material slightly, substituting a different
5 material, making a concentration change, adding something
6 else. It's to come up with the final composition that we
7 want oftentimes takes several attempts of matching the
8 correct material to give us in combination the material that
9 we would like.

10 Q. Is there tweaking that goes on?

11 A. There is tweaking that goes on.

12 Q. Okay. And have you looked at the submission that the
13 inventor made to the Patent Office?

14 A. Yes, I have.

15 Q. And we have that here. This is slide DDX-5.52 and
16 this is Exhibit DTX-114 at pages 3 to 4, and it's the
17 declaration of Ms. Malhotra. You understand that's one of
18 the inventors here?

19 A. Yes.

20 Q. All right. And you called out paragraph 9. Why
21 paragraph 9?

22 A. Paragraph 9 contains the description that the
23 inventor provided to the Patent Office where she described
24 the Example 3 in Cramer to be inoperable and unacceptable as
25 a pharmaceutical formulation.

Donovan - direct

1 Q. All right. And does she provide her reasons for why
2 she -- her observations as to why in her opinion it's
3 inoperable?

4 A. Points A, B and C are what she declared to be her
5 reason for her determination of inoperability.

6 Q. All right. So let's take those a step at a time
7 here.

8 She has an issue she characterizes as
9 unacceptable settling and difficulty in resuspending. And
10 it says, the homogeneity of the active material in product
11 is not expected to be maintained due to caking seen at the
12 bottom of the vial of the formulation.

13 Do you see that?

14 A. I see that.

15 Q. And have you evaluated whether that indicates to you
16 that this is an inoperable formulation?

17 A. It doesn't indicate to me that the formulation is
18 inoperable.

19 Q. Why not?

20 A. Well, in the case of settling, we anticipate
21 settling, and the inventor is not very -- very clear about
22 what difficulties that she had in resuspending in any
23 quantitative or measurable or even evaluative sense. So,
24 you know, settling is expected.

25 We can alter settling rates oftentimes

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1 with the thickener that we choose and so there would be a
2 way to tweak this formulation if necessary to account for
3 that settling and modify its behavior so it doesn't make
4 this unacceptable just because the one time the inventor
5 tried this and then evaluated it, determined in their eyes
6 that it was -- it was difficult and I don't know what that
7 means.

8 Q. Okay. And when you as a formulator see the term
9 unacceptable settling, are there steps that formulators know
10 to take, or as of 2002 knew to take to address issues like
11 unacceptable settling?

12 A. Certainly. There's a number of things that a
13 formulator might attempt to do to address the settling
14 rate.

15 Q. And --

16 A. -- of the suspension.

17 Q. And are those things that are within the level of
18 skill in the art?

19 A. Yes, they are.

20 Q. Of ordinary skill in the art?

21 A. Yes, they are.

22 Q. All right. Let's go to the second one.

23 If a person of ordinary skill in the art
24 saw an unacceptable -- well, let me ask you this question.
25 The inventor, Ms. Malhotra, says unacceptable jet rather

Donovan - direct

1 than desired spray mist, and I'm not going to read the
2 paragraph, but is the gist of the paragraph that the spray
3 or the fluid came out in a jet rather than a spray?

4 A. Yes. In essence, it had what we call a narrow cone
5 angle. It was very narrow that -- versus being broad that
6 may anticipate a spray to be.

7 Q. Okay. Does that indicate to you that this was a
8 formulation that was inoperable?

9 A. No, it does not.

10 Q. Why not?

11 A. Well, in the case of their observation for B, the
12 inventor took the Cramer composition and put it into a spray
13 container to spray it. A person of ordinary skill in the
14 art understands that there's a coordination between the
15 formulation and the spray container and spray device, that
16 you select various devices to potentially give you the
17 performance or you alter your formulation slightly to be
18 compatible with a device to give the shape of the emitted
19 spray that you would like.

20 And so this -- I don't find jets to be
21 unacceptable personally, but if the inventor had desired a
22 different pattern to their spray, they could have easily
23 modified either the formulation slightly or selected a
24 different spray container and re-evaluated the system.

25 Q. And are those kinds of modifications that you just

1 referred to within the level of skill of a person of
2 ordinary skill in the art?

3 A. Yes, they are.

4 Q. All right. Let's go to the last one, unacceptable
5 osmolality. We've talked about this before but not using
6 these words. What is osmolality?

7 A. Osmolality is what the tonicity adjuster is
8 addressing, so osmolality, iso-osmotic, isotonic, not by
9 definition exactly the same, but in the case of a
10 formulation applied to the nasal mucosa, essentially the
11 same term. So in this case it's the number of solute
12 molecules dissolved in the vehicle and the inventor declared
13 that to be unacceptable.

14 Q. Okay. And as a person with expertise in formulation,
15 when you see unacceptable osmolality in a first formulation,
16 a first attempt, do you conclude that you have an inoperable
17 formulation?

18 A. No, I don't.

19 Q. Why not?

20 A. Well, I look -- because I know that the osmolality is
21 an effect of the materials I've put into solution and I go
22 back and re-evaluate the components of that initial
23 formulation and make a determination about whether I could
24 substitute something or whether I could reduce the
25 concentration of one of the components to then adjust the

1 osmolality if I found it to be a value that didn't meet my
2 desired target.

3 Q. Could a person of ordinary skill in the art faced
4 with osmolality that was considered unacceptable address
5 that issue?

6 A. Yes, they could.

7 Q. And how would they do it?

8 A. Well, again, they would -- they would make a slight
9 adjustment to the formulation and they would measure the
10 osmolality again and continue to make adjustments to the
11 formulation where they know that they would be removing
12 solute molecules from the selection, and that's either by
13 substituting other materials that would also perform in the
14 same way as what the material that's perhaps responsible for
15 increasing the osmolality.

16 Q. Okay. Does the testing that Ms. Malhotra is
17 commenting on in her declaration show a person of ordinary
18 skill in the art that this formulation could not make a
19 suspension and -- a formulation that included a suspension
20 of an active ingredient and an active ingredient that went
21 into solution in the same formulation?

22 A. No, it does not.

23 Q. Why not?

24 A. Well, again, she made it. She examined it. She
25 tested some things about that composition. So that Example

1 3 was successfully prepared.

2 MR. LOMBARDI: Your Honor, I could go right up
3 to the minute if you want.

4 THE COURT: Well, unless you think you're going
5 to be finished with the example in about two to
6 three minutes, it's probably a good point to stop.

7 MR. LOMBARDI: I don't think so, your Honor.

8 THE COURT: All right. Bear with us for a
9 moment. Let's just talk about where we are on my end and
10 where we are on your end.

11 I am scheduled to charge the jury in my other
12 case starting around 9:00 o'clock tomorrow morning. Based
13 on the estimate that counsel has given me for the length of
14 their closings, and you all know what those are worth, but I
15 think I may be available as early as 2:00 p.m. It will not
16 be before 2:00 p.m., but I would ask that you all be here
17 and be ready to go at 2:00. It may turn out that it's
18 closer to 3:00, 3:15. We'll just have to see how the day
19 goes with the jury.

20 I'm definitely available until 7:00 p.m.
21 tomorrow night whenever we start. Then on Friday, assuming
22 nothing unusual happens, I plan to be here at 8:30 a.m. to
23 get started and unclear at the moment quite how late I can
24 be here on Friday, but it will be until at least
25 5:00 o'clock, possibly later. And we still have Saturday in

1 the background if it turns out that we need it.

2 The next two days, of course, are all subject to
3 if the jury needs me, then I will need to run upstairs for
4 them.

5 All that said, I believe we're on the
6 defendants' last live witness?

7 MR. LOMBARDI: That's correct, your Honor.

8 THE COURT: Okay. And --

9 MR. LOMBARDI: In our case-in-chief. Of course.

10 THE COURT: Right. And it seems we're nearing
11 the end of the examination?

12 MR. LOMBARDI: We are, your Honor.

13 THE COURT: Okay. All right. And then roughly
14 speaking, plaintiffs, I know we have not started your case,
15 but how do you see that playing out at the moment?

16 MS. EVERETT: At the moment it obviously depends
17 on the schedule, but if we start tomorrow, Thursday, we
18 anticipate being able to finish sometime Friday.

19 THE COURT: Okay. All right. So depending on
20 availability, we may be able to get this done Friday.
21 Right?

22 MR. LOMBARDI: It's possible, your Honor.

23 THE COURT: Okay. All right. Well, we shall
24 see. Have a good evening. Thank you all very much. I will
25 see you tomorrow.

1 MR. LOMBARDI: Thank you, your Honor.

2 (Court adjourned at 7:00 p.m.)

3
4 I hereby certify the foregoing is a true and accurate
5 transcript from my stenographic notes in the proceeding.

6 /s/ Brian P. Gaffigan
7 Official Court Reporter
8 U.S. District Court
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